Association between Physical Activity and Alzheimer's Disease

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ABSTRACT

The literature available establishes association between physical activity and risk of Alzheimer's disease. The aim of this review was to systematically evaluate the evidence on the relationship between physical activity and Alzheimer's disease.

Medline via PubMed was searched for original research articles assessing association between physical activity and Alzheimer's disease. The review was limited to prospective observational and intervention studies. Criteria for exclusion was studies conducted on demented patients, cross-sectional study design and reports. The quality of studies was assessed in 5 domains of bias.

18 longitudinal observational studies were included in this systematic review. Of the 18 selected studies, 14 found a significant inverse association between physical activity and Alzheimer's disease, 9 of these 14 studies formed a moderate quality of evidence whereas 5 presented low quality evidence.

Of the total 18 studies, 4 studies found non-significant to no association. Out of these 4 studies, 2 formed moderate quality evidence and 2 formed low quality evidence. There appears to be an inverse significant association between physical activity and Alzheimer's disease supported by a moderate quality of evidence.

The results of this review suggest that physical activity is inversely associated with risk of Alzheimer's disease based on moderate quality of evidence. The optimal dose of physical activity to induce protection presently remains unclear and needs further investigation. Future studies should employ better study designs, include younger participants with objective physical activity measurement and have longer follow-up in order to improve the quality of the research.

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On Yksi Nimi Ylitse Muiden, Yksi Nimi Muuttumaton.
Yksi Nimi Ylitse Muiden, Vain Yksi Nimi Toivomme On.
Tuo Nimi, Josta Laulan On Jeesus,
Nimi Kaunein Alla Auringon

All hail the power of Jesus name! Let angels' prostrate fall; bring forth the royal diadem, and crown Him, Lord of all. To the Author and Finisher of my Salvation, my dear King who carries my burdens each day… Blessed are you my Lord, my Strength who teaches my hands to war, and my fingers to fight: my Goodness, and my Fortress; my high Tower, and my Deliverer; my Shield, and He in whom I trust... Lord! what is man, that You take knowledge of him? Or the son of man, that You think of him? (Psalm 144:1-3)

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My flesh and my heart may fail, but God is the strength of my heart and my portion forever.

(Psalm 73:26)

ABBREVIATIONS

Aβ:	Amyloid beta
ACE:	Acetylcholinesterase
AD:	Alzheimer's disease
APOE:	Apoliporotien E
APP:	Amyloid precursor protein
CAMDEX:	Cambridge Examination for Mental Disorders in the elderly
CASI:	Cognitive Ability Screening Instrument
CES-D:	Center for Epidemiologic Studies Depression Scale
CP:	Consensus Panel
CRP:	Serum C-reactive protein
CSF:	Cerebrospinal fluid
CT:	Computed Tomography
DM:	Diabetes mellitus
DSM:	Diagnostic and Statistical Manual of Mental Disorders
EOAD:	Early onset Alzheimer's disease
GDS:	Geriatric Depression Scale
GMS:	Geriatric Mental Schedule
HDS:	Hasegawa's Dementia Scale
IQCODE:	Informative Questionnaire on Cognitive Decline in the Elderly
LOAD:	Late onset Alzheimer's disease
MET:	Metabolic equivalent
MMSE:	Mini Mental State Examination
MRI:	Magnetic Resonance Imaging
NINCDS-ADRDA:	National Institute of Neurological Disorders and Stroke and the Alzheimer's disease and Related Disorders Association
NSAIDs:	Non-steroidal anti-inflammatory drugs
TBI:	Traumatic brain injury
TICS:	Telephone Interview for Cognitive Status

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1 INTRODUCTION

In the year 2010, 35.6 million people worldwide were considered to have dementia and this number is projected to reach 1.25 billion by 2050, accounting to 22% of the world's population[1]. This poses a great challenge to individual, society and economy. Therefore, it is necessary to explore means to promote mental health which would counter or delay the onset of ageing brain disorders.

Growing evidence links comorbid, psychosocial, etiologic and life style factors to Alzheimer's disease (AD) [2]. Of these, physical activity may contribute to prevention of cognitive decline and delay the onset of AD. Physical activity is also known to have potential effects on general health and can significantly reduce the risk of heart attack, stroke and diabetes[3]. It can protect against these risk factors. Physical activity is essential for maintaining good blood circulation to the brain and encourage neurogenesis and synaptogenesis protecting against AD and other dementias[4]. Physical exercise is relatively easier to do and is most effective when done regularly. Oxygen consumption of the brain is improved by aerobic exercise and it benefits brain function; aerobic fitness has been found to reduce brain cell loss in elderly subjects[5]. Multi-faceted physical activities that also involve mental and social activity provide additional value for brain health.

One aspect of AD prevention in the near future may be based on principles governing lifestyle habits such as diet, cognitive activity and physical activity[2]. This systematic review was conducted to study the role of physical activity as a potentially preventive and cost-effective intervention against AD onset. Where other reviews have not gathered literature on physical activity and AD association specifically, this review served the purpose of compiling and consolidating evidence on this association in particular. Defining the optimal preventive and therapeutic strategies in terms of type, duration, and intensity of physical activity is an important practical question. It was also aimed to define a threshold for physical activity that could be protective towards the risk of AD.

No randomized controlled trials (RCTs) have yet demonstrated that regular physical activity prevents dementia. Biological research does provide accumulating evidence but better clinical interventional studies are needed to demonstrate this relationship. Epidemiological evidence on association between physical activity and AD is limited and is subject to many limitations. Therefore, a formal risk of bias assessment for the included studies was

performed and the quality of the studies was judged in domains such as exposure assessments, follow up years and sample selection. Thus, the quality of the evidence provided by the included studies was assessed. This review systematically analyzed the studies on association between physical activity and AD and assessed the quality of the available evidence.

2 LITERATURE REVIEW

2.1 Alzheimer's disease (AD)

2.1.1 Definition

Alzheimer's disease (AD) is the most common type of dementia. AD is characterized by a progressive decline in cognitive function which typically begins with deterioration in memory. Other signs of AD are difficulty in performing familiar tasks, problems with language, disorientation with respect of time and place, poor or decreased judgment, and problems with abstract thought, misplacing things, changes in mood and behavior, changes in personality, loss of initiative.[6]

The characteristic symptoms of mild AD are impaired episodic memory, deterioration of language, orientation and executive functions along with apathy and depression. Vocabulary shrinks with decreased word fluency and general decline in spoken and written language. The patients may continue to perform many tasks independently but with certain cognitively challenging activities, they require assistance or supervision.[7]

Those with moderate AD have speech difficulties, impaired long term memory, behavioral and neuropsychiatric issues arise accompanied by wandering, irritability, aggression burst. The severe stage of AD renders the patient completely dependent upon caregivers. Patient experiences extreme apathy and exhaustion. Language skills are lost to a single word or at times to a complete loss of speech. They may not be able to perform most basic tasks without assistance. They mostly remain bed-ridden and unable to feed themselves; disability leads to institutionalization, and decreased quality of life. Life expectancy is shortened.[8] The typical clinical duration of the disease is eight to ten years.[7]

2.1.2 Clinical Diagnosis

The diagnosis of AD is clinical, based on signs of slowly progressive cognitive decline and findings of cerebral cortical and hippocampal atrophy on neuroimaging. The clinical diagnosis is correct approximately 80%-90% of the time.[8]

The DSM-IV criteria (American Association 1995) is used for early AD diagnosis. In general the current diagnostic criteria are characterized by two step procedure: (1) Identification of a dementia syndrome (2) exclusion of other etiologies of dementia syndrome, using biological and neuroimaging examinations. According to the DSM the essential feature of dementia are

memory impairment, one or more cognitive disturbances such as aphasia (language disturbance), apraxia (impaired ability to carry out motor activities despite intact motor function), agnosia (failure to recognize or identify objects despite intact sensory function), disturbances in executive functioning (planning, organizing, sequencing, abstracting). In addition the cognitive decline causes significant impairment in social or occupational functioning and presents a decline from a previous level of functioning.[9]

New diagnostic criteria for AD/early AD requires neuropsychological testing, cerebrospinal fluid (CSF) testing and magnetic resonance imaging (MRI). Through this it is possible to identify AD with high accuracy, even in the early stages of the disease. This captures both the prodromal and the more advanced dementia stages of the disease in the same diagnostic framework.[10]

The NINCDS-ADRDA Alzheimer's Criteria is widely used in research. The presence of cognitive impairment and a suspected dementia syndrome confirmed by the neuropsychological testing are needed for a clinical diagnosis of possible or probable AD. Also, histopathological confirmation is required for definitive diagnosis. Eight cognitive domains: memory, language, perceptual skills, attention, constructive abilities, orientation, problem solving and functional abilities are checked for impairment.[11]

CERAD is recommended for cognitive screening. This battery consists of 6 tests: Verbal Fluency: Animal Category, a short form of the Boston Naming Test, Mini-Mental State Examination (MMSE), Verbal Memory Test consisting of word list learning, delayed recall, a recognition procedure and Constructional Practice (including delayed recall), and clock drawing test.[12] For clinical and more comprehensive evaluation, neuropsychological testing is often used.

Laboratory evaluations include a full blood count, electrolytes, blood glucose, liver function test, renal function test, calcium, phosphates, thyroid function test, vitamin B-12, folate, electrolyte sedimentation rate and C-reactive protein. For structural brain imaging, magnetic resonance imaging (MRI) or computed tomography (CT) scan are also performed. Cerebrospinal fluid (CSF) biomarkers are used for early AD diagnosis and genetic testing is rarely used in some cases.[13]

2.1.3 Neuropathological Findings

AD is characterized by loss of neurons and synapses in the cerebral cortex and certain subcortical regions. According to amyloid cascade hypothesis beta-amyloid (Aβ) deposits

have a key role in AD.[14] The deposition of Aβ is the initial pathological trigger in the disease, which subsequently leads to the formation of neurofibrillary tangles, neuronal cell death and dementia. There exists considerable evidence supporting this hypothesis, however, there are observations that seem to be inconsistent. AD is also considered as a taupathy due to abnormal aggregation of tauprotein.[15] Tau (micro-tubule associated protein, major component of the neurofibrillary tangle) is a significant pathological substrate of AD since tau tangles have a more close association with degree of dementia than Aβ plaques.[16]

Macroscopically, hippocampal atrophy is the starting point of the pathogenesis of AD; brain tissue shrinks with AD progression. The ventricles, are noticeably enlarged. In the early stages of AD, short-term memory begins to decline with the degeneration of hippocampal cells or hippocampal atrophy[17].Volume is most notable on coronal sections with shrinkage of medial temporal lobe structures including hippocampus. There is enlargement of the temporal horns, as well as of the third and lateral ventricles.

Evidence shows that hippocampal atrophy has functional consequences like cognitive impairment. The deposition of tau protein, formation of neurofibrillary tangles and accumulation of amyloid β (Aβ) contributes to hippocampal atrophy.[18,19]

The spread of AD through the cerebral cortex worsens judgment, outbursts emotions and impairs language. Advancement of the disease leads to the death of more nerve cells resulting in subsequent behavioural changes like wandering and agitation.[20]

2.1.4 Epidemiology

AD accounts for 70% of all cases of dementia. It is estimated that 7.7 million new cases of dementia occur every year in the world, accounting to more than 35.5 million people living with dementia in 2010. Since one new case of dementia occurs in every 4 seconds, the number of people with dementia is expected to double every 20 years and to reach 90.3 million by the year 2040.[1]

High prevalence of dementia occurs in China and its western Pacific neighbors (6 million), in the U.S (5.5 million), with the European Union (5 million) and India (1.5 million) next in line. It is predicted that between 2001 and 2040, there will be 100% increase in dementia cases in the developed countries whereas a 300% rise in India, China and other south Asian and western Pacific countries. [21] The global prevalence of dementia among people of age 60 years and older is calculated to be 4.7% with region specific prevalence being: 2.6% for Africa, 4.0% for Asia, 6.2% for Europe (AD prevalence 4.4%), and 6.9% for North

America.[22] Although two thirds of all persons with dementia live in developing countries, yet only 10% or less of population based, dementia related research has been conducted in those regions[23]. The magnitude of the impending rise owing to societal aging is considerable and will be a costly public health burden in the years to come.

Cases of AD have been described as early as the third decade but the majority of cases occurs after the age of 65 years. The prevalence of AD doubles each decade from 5% before age 65 years to nearly 50% at age 85 years.[14] It remains inconclusive whether the risk continues to increase after the age 85. However, in brain ageing over 90 years, the pathology often is characteristic of AD; but the disease progression is much slower in oldest old compared to those who develop the disease at younger ages.

The quality of data varies between studies and thus regional differences in the age-specific prevalence pose a question whether these differences are real or they result from different methodologies.[24]

2.1.5 Impact

For a person knowing, he has AD, is a personal catastrophe. The disease affects independence, relationships and the ability to express oneself. They eventually lose sense of who they are and the ability to care for themselves.

During the early and middle stages of AD, depression is very common, drawing them to isolation. The mood and personality of AD patients changes and they become more confused, suspicious, depressed, fearful and anxious. In various settings like at home, at work or during social engagement they easily become upset when out of their comfort zone. Memory loss disrupts daily life; they face challenges in planning or solving problems, performing familiar tasks, following or joining a conversation, coping up with work or social activities. Younger individuals with the disease can also face other issues, if working, they may have to reduce work hours or quit, leaving a gap in the family income. Dementia causes an individual to spend 11.2% years of life with disability whereas stroke contributes 9.5%, musculoskeletal diseases 8.9% and cardiovascular diseases 5.0% to years lived with disability. AD is thus, potential cause for functional disability and institutionalization. [25] Excessive risk of death among older individuals is attributable to AD to a similar extent as that of malignant tumours. AD is associated with a two to fivefold risk of death. The relative risk for mortality associated with AD is 2.6 which however gets weaker after adjusting for comorbidities. Median survival for newly diagnosed cases with AD ranges from 3 to 6 years. Shorter

survival is predicted in AD patients with old age, male sex, low education, comorbidities like hypertension, diabetes and heart disease, poorer cognitive function and physical disability.[26]

Generally family provides care to the older people who have lost the capacity of independent living. In developed countries, the crucial caring role of family is often overlooked since the health and social care system is efficient whereas in the developing countries, the role of the family is often overestimated. However, many carers experience high levels of strain, psychological morbidity and possibly impaired physical health. Behavioral and psychological symptoms of the patients affect the quality of life of carers the most. Many studies report very high levels of psychological morbidity amongst carers, the EUROCARE estimates are 40% to 75%[27]. In the US, more than 40% of family and other unpaid carers of people with dementia report high to very high emotional stress [28]. Prolonged stress and physical demands of the work, along with the biological vulnerabilities of the old carers predisposes them to risk of physical health problems. In spite of the facilities of high level care in the high income countries, about 10 million people i.e. family, friends, neighbors in the US provide unpaid care for people with other dementia or AD [2]. In the US, AD and dementia caregivers had $9.1 billion in additional health care costs of their own in 2012. [29] In Europe, 85% or more couples (one suffering from dementia, the other being carer) lived on their own. Whereas, according to 10/66 pilot studies in the developing world, people with dementia mostly live in joint family systems [30] since informal home care is usually the only source of care available to them[2]. Moreover, the role of women and family in care-giving is getting less common due to increasing challenges of education and work. Trends like migration, declining fertility (in the final stage of demographic transition) such as in China; people are aging rapidly and this impacts the care provided to patient [29].

The rapid increase in the number of patients with dementia and AD pose a tremendous challenge to society and economy signified by the current number of AD patients estimated to quadruple in the coming three decades[2]. About 43% of the patients with dementia require institutionalized care. In industrialized countries, majority of the patients residing in the nursing homes suffer from dementia. In the coming years is predicted to be the main cost for developed countries and enormous resources will be needed for the AD and dementia patient care. AD is estimated to be the third most expensive disease after cardiovascular disease and cancer in terms of direct and indirect cost. The former contribute more to mortality rather than disability. The economic impact will continue to grow as the population ages, and the number of AD patients increase.[14]

The total estimated worldwide costs of dementia were $604 billion in 2010, these are projected to rise by 85% in coming two decades[31]. The US in 2012, had 15.4 million family and friends providing 17.5 billion hours of unpaid care to those with AD and other dementias care valued at $216.4 billion, which is more than eight times the total sales of McDonald's in 2011[29]. Eighty percent of care provided in the community is provided by unpaid caregivers. The total costs of dementia care in U.S alone are projected to be more than double by 2040, to a range of $379 billion to $511 billion, from $159 billion to $215 billion in 2010.[32]

2.1.6 Risk Factors

2.1.6.1 Genetics

Early-onset AD (EOAD) occurs in people aged <65 years. This represents less than 5% of all AD cases. Where some EOAD cases have no known cause, these cases are referred to as familial AD.[33]

EOAD is caused in some by autosomal dominant mutations at three genes amyloid precursor protein (APP) presenilin 1(PSEN1) and presenilin 2 (PSEN2) coding for proteins involved in APP breakdown and Aβ generation. EOAD is clinically indistinguishable from late-onset AD (LOAD) and is generally associated with a more rapid rate of progression and a Mendelian pattern of inheritance. The γ secretases which cleaves APP to produce Aβ consist of the presenilin proteins and thus these mutations affect concentrations of $A\beta_{1-42}$. Chromosome 10 is thought to have another familial gene for AD.

APOE is a lipid-binding protein and is expressed in humans as three common isoforms coded for by three alleles, APOE ε 2, ε 3, and ε 4. APOE is consistently associated with AD and is the only established genetic factor for both EOAD and LOAD [2]. There is a seven fold risk in individuals with two APOE ε4 alleles compared to those with APOE ε3 alleles. It is a susceptibility gene for AD without being a necessary or sufficient cause for developing AD. With increasing number of APOE ε4 alleles the risk of AD increases and the age of AD onset decreases in a dose dependent manner. Approximately 15% to 20% of AD cases are attributable to the ε4 allele and the risk effect of APOE ε4 allele on AD decreases with increasing age.

In patients with APOE genotype other candidate genes like TOMM40 gene located on chromosome 19 interacts with APP and is thought to influence the age of onset of AD (late-

onset). Polymorphisms of phosphokinases, such as DYRK1A, located on chromosome 21 (involved in tau phosphorylation) are thought to be associated with an increased risk of AD.

LOAD onset ≥ 65 years accounts for more than 95% of cases with AD. The genes involved in LOAD increase disease risk in a non-Mendelian fashion. First-degree relatives of patients with LOAD have twice the expected life-time AD risk of people without an AD-affected first-degree relative.[34] However, the relevance of these links in the clinical practice is not large.

Most of the AD cases are sporadic and there is heterogeneity considering the risk factor profile and neuropathological features. Both genetic and environmental factors direct the course of developing AD.[2]

2.1.6.2 Cardiovascular Factors

Hypertension is a cardiovascular risk factor which precedes AD by decades, but blood pressure decreases the years before dementia onset and is lower in individuals with AD than in controls as reported by several studies. High blood pressure has also been related to the neuropathological manifestations of AD. Hypertension couples with other vascular risk factors, including diabetes mellitus, obesity, and hypercholesterolemia. Also, these risk factors have been related to AD. The exact mechanism regulating these associations is unclear. Hypertension can lead to cerebrovascular disease which may express dementia syndrome in patients with AD encephalopathy. However, hypertension can accelerate the AD process and subclinical AD may lead to increased blood pressure. Similar biological mechanisms may be involved in the pathogenesis of both disorders. Hypertension is a risk factor for stroke, ischemic white matter lesions, silent infarcts, general atherosclerosis, myocardial infarction and cardiovascular morbidity and mortality. This risk increases with increasing blood pressure also at blood pressure within the normal ranges, and a high percentage of these cardiovascular events occur in those with normal blood or mild hypertension which in turn can cause neurological impairment. [35]

Several observational studies provide evidence linking uncontrolled mid-life hypertension to increased risk of dementia in late life.[36,37] However, various follow up studies have provided inconsistent results studying late life blood pressure in relation to risk of dementia like those with relatively short follow-up such as less than 3 years. These studies either have found no association or negative association. The negative association may result due to long latency period of dementia, having low blood pressure as the preclinical phase of the disease or its

consequence. But, certain studies with longer follow up period (follow up > 6 years) report inverse association, suggesting that low blood pressure may contribute to the clinical expression of AD.[38,39] The association between blood pressure and incident AD was significant in untreated diastolic hypertension [37].

Considering antihypertensive drugs, there is a protective effect of use of anti-hypertensive drugs against dementia and AD. This may depend on the duration of treatment and age when people receive their medication therapy. The efficacy was seen in people less than 75 years of age. It may work through the mechanism of postponing atherosclerotic process, reducing the number of cerebrovascular lesions and improving cerebral perfusion[40]. Also, calcium channel antagonists may have neuroprotective effects[41].

Evidence supports that certain components of renin angiotensin system may have a significant role in learning and memory processes. Angiotensin converting enzyme (ACE) is overexpressed in the hippocampus, frontal cortex, and caudate nucleus of AD patients. Brain distributing ACE inhibitors have been reported to rescue neuronal damage and improve behavior in animal models[42]. Brain penetrating ACE inhibitors can reduce the incidence of AD in elderly hypertensive patients. Treatment with brain penetrating ACE inhibitors could slow the rate of cognitive decline in mild to moderate AD patients in comparison with other antihypertensive drugs. The favorable effect might be due to direct effects of brain penetrating ACE inhibitors on renin angiotensin system in the brain. Moreover, an increased level of brain substance P by ACE inhibitors could be a possible mechanism; this substance P can augment the activity of neprilysin, a major amyloid β peptide degrading enzyme in the brain and thus may favorably influence the course of AD[42]. Another study in males found that angiotensin receptor blockers are associated with a significant reduction in the incidence and progression of AD and dementia compared with ACE inhibitors or other cardiovascular drugs in a predominantly male population.[43]

High serum cholesterol at midlife presents a greater risk of developing AD in the late life (20 years later), but decreasing serum cholesterol after mid-life may reflect an ongoing disease process and may act as a marker for late life AD[44]. Plasma cholesterol levels and amyloidogenesis are closely correlated as shown by in vivo studies [45]. They suggest that increase in dietary cholesterol intake boosts amyloid β (Aβ) levels and causes extensive deposition of senile neuritic plaques in the brain tissue. The Hisayama Study found that

abnormal lipid metabolism and dyslipidemia increased the risk of plaque-associated pathology and AD. [46]

Several cross sectional and case control studies show a reduced prevalence of AD among statin users. Whereas still other prospective studies report either no beneficial effect or only very little decreased risk of AD related to statin use. Certain neuropathological studies of AD subjects using statins indicate that statins inhibit inflammation in humans but might not reduce cerebral Aβ load. Other experimental studies show that statins may reduce the risk of AD through neuro-protective effects including endothelial protection through nitric oxide synthase system, antioxidant, anti-inflammatory and antiplatelet effects. Statin therapy is thought to reduce the risk of late-onset AD (LOAD) by almost 50 %.[47]

Diabetes mellitus (DM) is another major risk factor AD. Midlife or a longer duration DM plays a crucial role in dementia and AD[48,49]. In very old people prediabetes or impaired glucose tolerance is associated to an increased risk of dementia and AD. It is reported that newly diagnosed DM is associated with increased risk of future AD development. Also, increasing risk of AD is found to be associated with duration of DM suggesting DM may play an important role AD pathogenesis.[50] This may result from long term direct effect of uncontrolled hyperglycemia on neurodegenrative changes in brain or through several DM-specific factors, compounding detrimental effects on the central nervous system and adding to the burden of small-vessel disease Another interpretation of this association could be due to the effect of hyperinsulinemia or impaired insulin response or due to diabetes related comorbidities such as hypertension and dyslipidemia. A meta-analysis identified an association between DM and risk of AD, vascular dementia, and all-cause dementia. The risk of AD increased by 40% in diabetic patients. An APOE e4 allele further increased the risk of AD in diabetics.[51] The presence of an e4 allele doubled the relative risk of dementia in diabetics compared to participants with either of these risk factors.[52]

Anti-diabetic monotherapy is associated with a decreased AD risk whereas combination therapy using non-sulfonylurea insulin secretagouge, and either monotherapy or combination with insulin is associated with an increased AD risk[50]. Other evidence shows that neither monotherapy nor combination therapy with oral anti-diabetic drugs is associated with the risk of AD after adjusting for underlying risk factors and the duration of DM. This may suggest that it is DM or underlying comorbidities, not hypoglycemic agent that importantly determine future risk of AD. Insulin sensitizers may have beneficial effects on AD, and these benefits

may be counterpoised later by longer exposure to DM[53,54]. It can be inferred that duration of DM may play an important role in AD pathogenesis. Combination therapy with insulin has been found to be associated with greater risk of AD. The Rotterdam Study found diabetic patients treated with insulin were at the highest risk for dementia. Since combination therapy with insulin may represent greater severity of DM, these patients were at increased risk for AD.[55]

Cerebral and cardiovascular disease is a risk factor preceding AD. Cardiovascular diseases were associated with an increased incidence of dementia and AD as shown by Cardiovascular Health Study, with highest risk of dementia being seen in people with peripheral arterial disease suggesting that atherosclerosis is a risk factor for AD.[56,57] Stroke and silent brain infarcts and white matter hyper intensities seen on magnetic resonance imaging scans increased the risk of dementia and AD significantly.[58,59]

Other cardiovascular conditions such as atrial fibrillation, heart failure and more severe atherosclerosis measured with ankle to brachial index have been related to dementia and AD. Cerebrovascular lesions, atherosclerosis, and neurodegenerative changes in the brain often coexist, and may be coincident processes synergistically damaging the aging brain and promoting the clinical expression of the dementia syndrome.[60]

Understanding causal relationship between cerebral vascular disease and AD is complex owing to the long latency period between pathologic changes and clinical symptoms which may account to decades both in vascular disease and AD. However, an increase in the Aβ can lead to changes in cerebrovascular structure and function; increasing blood pressure, decreasing the amount of vascular endothelial cells, impairing vascular function, decreasing cerebral blood flow and resulting in further neurodegeneration.[60]

2.1.6.3 Depression

Depression particularly developing in late life appears to be prodromal symptom of AD[14]. Most of the neurobiological changes associated with depressive episodes and the vulnerability for recurrence constitute risk for AD. The interaction between stressful life events and genetic liability are thought to precipitate multiple depressive disorder. The negative loop of stress response may be manifested as an increment in cognitive dysfunction causing further exacerbation of these changes, increasing the risk for the development of AD. The individuals with a genetic liability for AD, via this detrimental cascade may have the initiation of AD pathology.[61]

Several studies have reported association between depression and elevated risk of dementia and AD over the 17-year evaluation period. [62-64] People with a history of depression had about a two times increased risk of dementia compared with those without a history of the disease.[65]

Several studies have shown significant correlations between depression and the risk of developing AD; the frequency of depressive episodes appears to be an important factor.[66] Also, there has been found a continuous relationship between the level of depression and the likelihood of developing dementia and AD. The risk of developing dementia increased by almost 50% for every 10-point increase in the Center for Epidemiologic Studies Depression **(**CES-D) Scale.[65]

2.1.6.4 Life Style Risk Factors

Smoking and its association with AD has been studied and previously cross-sectional studies have shown lower prevalence of AD amongst smokers compared to the non-smokers[67]. But, these results were subject to selective survival bias related to smoking since smokers are less in number amongst the prevalent cases. It has been argued that nicotine may be acting on cortical mechanisms involved in visual perception and attention, and supporting that acetylcholine transmission modulates vigilance and discrimination. Nicotine may therefore be of some value in treating deficits in attention and information processing in AD patients.[68] However, smoking has adverse effects on cardiovascular system which in turn is related to AD pathology. Recent cross-sectional studies have found an increased risk of AD associated with smoking especially among the non-carriers of APOE ε4 allele[69]. Meta-analyses of follow up studies concluded that current smoking was associated with increased AD risk nearly doubling the risk of AD.[70,71]

Light-to-moderate alcohol consumption reduces the risk of coronary heart disease and stroke[72]. Because vascular disease is associated with cognitive impairment and dementia, it is hypothesized that alcohol consumption might also affect the risk of dementia[73]. Light-to-moderate alcohol consumption is associated with a reduced risk of dementia in individuals aged 55 years or older whereas heavy drinkers at middle age had more than threefold risk of dementia and AD in late life, especially APOE ε4 allele carriers.[74] Light to moderate alcohol consumption has been shown to have a protective effect towards developing AD.[75,76] Excessive alcohol drinking has deteriorating effects on brain and even light to moderate alcohol drinking has been related to increased brain atrophy and smaller brain volumes.[77,78] It

is reported that weekly consumption of wine one to six or more than two drinks per week or more than three drinks i.e. 250-300 ml per day; in case of males, one to three drinks a day are protective towards the risk of developing AD.[76,79] Certain bioactive grape-derived polyphenols may protect against AD-type cognitive deterioration, in part by interfering with the generation and assembly of Aβ peptides into neurotoxic oligomeric aggregated species.[80]

Obesity is seen to have a direct association with AD. Higher midlife BMI (>30 kg/m2) is a risk factor for AD and dementia 20-25years later[81-85]. However, studies show that declining BMI in later life can predict dementia as shown by long term follow up study of Japanese American men, who experienced a decline in BMI, 10 years before the onset of dementia[86]. The results from another study show an age-dependent BMI-dementia related relationship, with higher BMI at midlife being a risk factor for developing dementia and decreasing BMI after the age 65 causing an increased risk of dementia.[85] But, the declining BMI at later age may be looked upon as a preclinical feature of AD.[2] The deleterious effects of obesity on cardio and cerebrovascular system are well known. It leads to insulin resistance that in turn causes diabetes, hypertension and cardiovascular abnormalities. The vascular effects of obesity may have a role in the development of AD.[87]

Increased dietary or supplemental intake of antioxidants like Vitamin E and C is associated with decreased risk of AD[88,89]. Oxidative stress is primarily a central feature of AD. Studies investigating adherence to a particular type of diet suggest that higher adherence to a diet with fruits, vegetables, fish rich in antioxidants especially “Mediterranean diet” is associated to reduce risk of AD independent of vascular pathways[90]. Vitamin B-12, folate, homocysteine associated to risk of dementia and AD gives mixed results. According to a Cochrane systematic review, vitamin B 12 and folate have no benefits on cognition though vitamin B12 plus folate are effective in reducing serum homocysteine[91]. Diet rich in saturated fats and cholesterol increase the risk of AD whereas the polyunsaturated fatty acids and fish may be protective against dementia.[92,93] Unsaturated fatty acids may confer protection through anti-inflammatory properties. Fatty acids have a role in synthesis and fluidity of nerve cell membrane s and for synaptic plasticity and neuronal degeneration, Also, coffee drinking at midlife is associated with a decreased risk of dementia/AD later in life. Coffee drinkers at midlife had lower risk of dementia and AD later in life compared with those drinking no or only little coffee adjusted for demographic, lifestyle and vascular factors, APOE Ɛ4 allele and depressive symptoms. The lowest risk (65% decreased) was found in people who drank 3–5 cups per day[94].

2.1.7 Etiologic Factors

2.1.7.1 Inflammation

Inflammatory markers may reflect both peripheral disease and cerebral mechanisms related to dementia; these processes are measurable long time before dementia manifestation. A higher level of serum C-reactive protein (CRP) in midlife was linked to an increased risk of AD and vascular dementia[95]. Follow up studies of older adults have shown an association between increased serum inflammatory markers, like CRP and interleukin-6, and higher incidence of dementia and AD.[96,97]

The nonsteroidal anti-inflammatory drugs (NSAIDs) used greater than two years may have beneficial effect against AD and dementia[98]. Experimental research found that neuritic plaques in brain are associated with inflammatory proteins. Thus, it seems valid to hypothesize that inflammatory mechanisms may play a role in the processes leading to neurodegeneration. However, the neuropathological studies found no evidence for an association between use of NSAIDs and reduced burden of AD pathological changes. Moreover, an increased risk for AD was found with the drug therapy in the clinical trials of anti-inflammatory drugs (celecoxib or naproxen).[99] NSAIDs have an adverse effect in later stages of AD pathogenesis, while asymptomatic individuals treated with conventional NSAIDs like naproxen experience reduced AD incidence, but only after 2 – 3 years. Thus, treatment effects differ at various stages of disease.[100]

However, NSAIDs are associated with a number of adverse effects including alterations in renal function, effects on blood pressure, hepatic injury and platelet inhibition which may result in increased bleeding. However, the most important adverse effects of NSAIDs and COX-2 inhibitors are the gastrointestinal and cardiovascular adverse effects, respectively. The deleterious gastrointestinal effects of NSAIDs are cause for concern because of their frequency and seriousness. Therefore, in geriatric population NSAIDS should be used with caution. Recent clinical trials have also shown an apparent increased risk of cardiovascular adverse events in patients taking COX-2 inhibitors.[101]

2.1.7.2 Toxic exposures

Manual work as a life time occupation is associated to risk of developing AD. This suggests a possible implication of occupational toxic exposures in the risk of developing dementia disorders[102]. Heavy metals like aluminum and mercury have been suggested as a risk factor for AD. Moreover, follow up studies associate extremely low frequency electromagnetic

fields (ELF-EMF) with increased risk of AD and dementia[103,104]. Forms of electromagnetic include gamma rays, X-rays, ultraviolet radiation, visible light, infra-red radiation, microwaves and radiofrequencies. Occupations with typical exposures to ELF-EMF include electric power installers and repairers, power plant operators, electricians, electrical and electronic equipment repairers, telephone line technicians, installers and repairers and workers operating electrical equipment such as welders, carpenters and machinists.[105]

2.1.7.3 Traumatic brain injury

Traumatic brain injury (TBI) has been widely investigated as a possible risk factor for AD. There is an association between a history of previous head injury and risk of developing AD according to a meta-analysis of case control studies.[106] Some longitudinal studies found the positive association only with severe head injury[107,108]. Around half of those who have a TBI cut down on their drinking or stop altogether after injury, but some people with TBI continue to drink heavily, which increases their risk of having negative outcomes like getting injured again, worsening of cognitive impairment and increased chances of having emotional problems such as depression.

Alcohol use and traumatic brain injury (TBI) are closely related. Up to two-thirds of people with TBI have a history of alcohol abuse or risky drinking. Between 30-50% of people with TBI were injured while they were drunk. Moreover, drinking can reduce brain injury recovery.[109] These factors contribute to neurological impairment and have an indirect contribution to AD pathology.

2.1.8 Psychosocial Factors

2.1.8.1 Education

Low education may also increase the risk of AD whereas better education attainment is reported to protect against the clinical manifestation of dementia/AD even in APOE ε4 carriers.[110,111]

Education, as a socializing process promotes certain lifelong learning strategies, encouraging individuals to develop forms of decontextualized thinking. Evidence shows that lifestyle characterized by engagement in leisure activities of intellectual and social nature is associated with slower cognitive decline in healthy elderly population and may reduce the risk of incident dementia[112].

Education along with occupation is a marker of cognitive reserve and has been linked with lesser risk of incident dementia. It is not because of any reduction in dementia-related neuropathology, but due to an increase in the threshold at which these pathological changes are clinically manifested[113]. It has been found through structural MRI analysis for cortical thickness and brain volume that more years of education increase the threshold before which brain atrophy clinically manifests in AD patients.[114]

Individuals with higher education have been found resistant to the harmful effects of white matter lesions on cognition[115]. Also, high cognitive reserve has been shown to protect against the progression from normal cognition to the onset of AD clinical symptoms independent of amyloid levels in CSF but was associated with low levels of tau and phosphorylated tau[116]. Moreover, education being a key element of cognitive reserve, in particular develops the brain's language systems.

2.1.8.2 Social Networking

Social disengagement has been associated with cognitive decline. There is increased risk of dementia and AD in older people with increased social isolation. Evidence is present that low neuroticism along with high extraversion was the personality trait associated with decreased risk of dementia. Among the socially isolated individuals, even low neuroticism alone seemed to minimize the risk. Low social engagement from middle age to late life doubles the risk of AD and dementia in late life. Rich and large social networks provide effective and intellectual stimulation that could influence cognitive function and different health outcomes through behavioral, psychological and physiological pathways.[132, 141]

2.1.8.3 Mental Activity

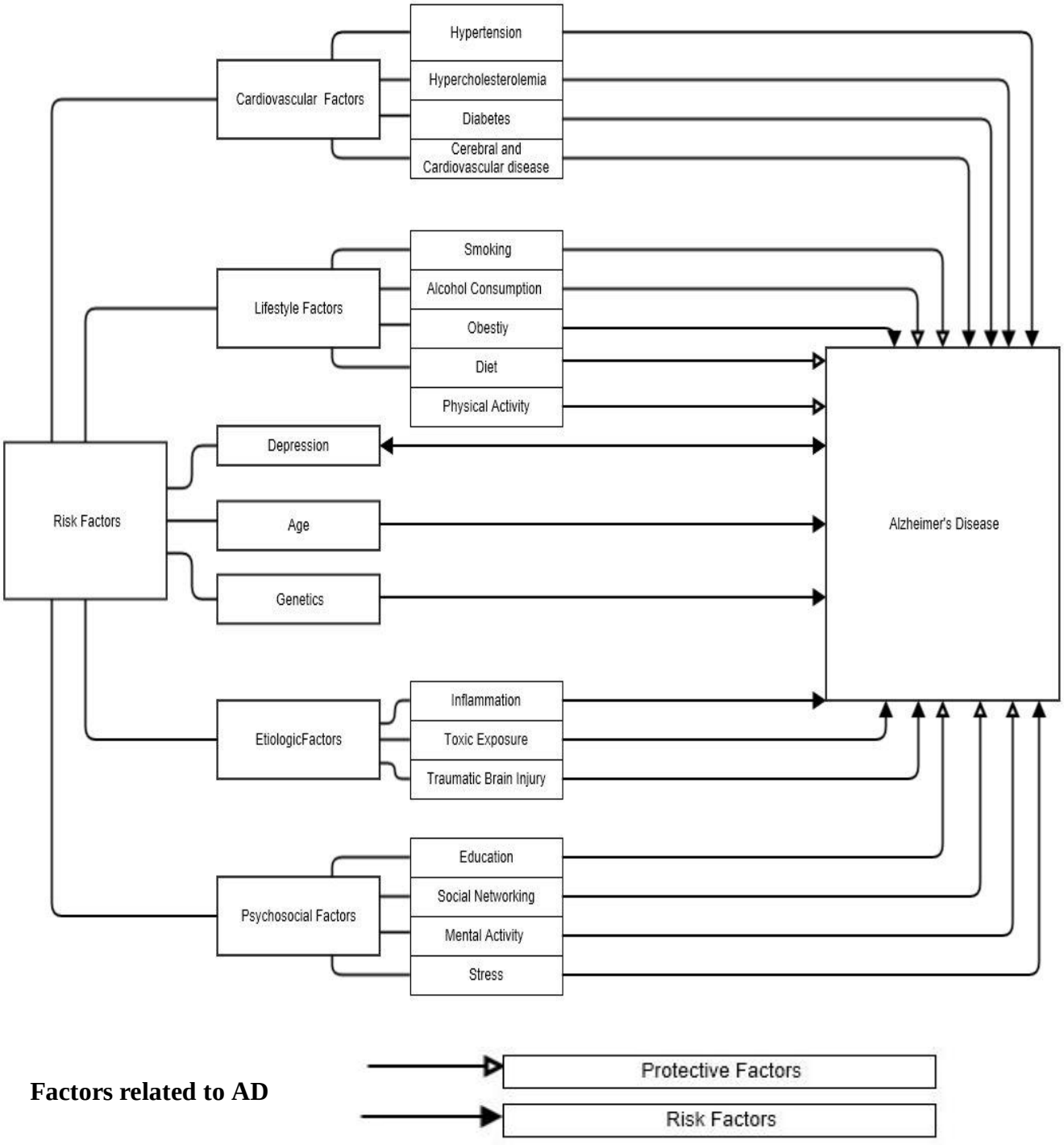
Many studies have examined mentally demanding activities in relation to dementia and AD including knitting, gardening, dancing, playing board games, musical instruments, reading, social and cultural activities, watching certain television programs[51,117]. Most of them show a protective effect. The Swedish Twin Study showed an inverse association of risk of AD development and complexity of work[118]. A neuroimaging study suggests that there is reduced rate of hippocampal atrophy with the complex mental activity. The process of mental stimulation may play a role in preserving cognition. Since it involves thinking and attention control processes which might increase brain reserve in old age. Cognitive performance may be enhanced because of continual participation in intellectually challenging activity.

The neurotransmitter noradrenaline offers a candidate mechanism mediating between reserve and reduced risk of AD[119]. Strong support for such a protective role of noradrenergic activity has emerged in a recently[120]. Repeated noradrenergic activation over a lifetime may therefore enhance brain reserve both by synaptogenesis and neurogenesis effects, as well as by protecting other crucial neurotransmitter systems such as dopamine and noradrenaline. Noradrenergic activity may actually suppress the accumulation of amyloid plaques in the brain, reduce their aggregation, or diminish the inflammatory toxicity of amyloid to the surrounding cells as shown by studies in animal models[121].

2.1.8.4 Stress

Lifelong work-related psychosocial stress, characterized by low job control and high job strain, has been associated with increased risk of dementia and AD in late life, independent of other known risk factors[122]. Studies have also found association between psychological stress in middle-aged women and development of dementia, especially AD[123].

Stress causes impairment in memory performance and it is pathophysiologically related to AD. The stress-sensitive hippocampus is a structure which normally plays a crucial role in the storage of various events in long-term memory. Hippocampal atrophy is thought to be involved in pathophysiology of neurodegenerative mechanisms and their association with stress[31]. Hippocampal activity is blocked leading to a loss of neurons particularly in the hippocampal area and stress leading to deterioration of memory performance. Also, aging hippocampus is more susceptible to stress and this vulnerability may yet be increased in AD. The hypothalamus-pituitary-adrenal axis activation due to stress may represent a starting point of memory loss. As stress and arousal levels increase, learning and memory deteriorate accordingly classic inverse U-shaped curve.[124]



Factors related to AD

Figure 1. Factors related to Alzheimer's Disease

2.2 Physical Activity

2.2.1 Definition

Physical activity is defined as any bodily movement produced by contraction of skeletal muscles that requires energy expenditure substantially more than resting energy expenditure[125]. Physical activity includes exercise as well as other activities which involve bodily movement and are done as part of playing, working, active transportation, house chores and recreational activities. The physical activity ranges from light physical activity to moderate to vigorous physical activity. In geriatric population, light physical activity involves energy expenditure about 1.6-2.9 Metabolic Equivalent (MET). It includes activities such as slow walking and is close to sedentary behavior. The energy expenditure of 3-6 MET[126,127] characterizes a physically active behavior or discretely known as moderate to vigorous physical activity. The very old community dwelling people who have sedentary behavior or light physical activity ≤ 2 times a week are considered to be inactive. Whereas the ones with physical activity > 2 times a week (light, moderate or vigorous) are considered to be active.

An example of practically assessing the intensity or frequency of physical activity is Grimby scale which is subjective relying on questionnaires asking the participants: "Which of the following options describes best your present physical activity?" They are given seven response options: no other physical activity than normal activities of daily living (0), light physical activity e.g. walking one to two times a week (1), light physical activity e.g. walking several times a week (2), moderate physical activity that causes some shortness of breath and sweating one to two times a week (3), moderate physical activity that causes some shortness of breath and sweating several times a week (4), moderate or vigorous physical activity that causes quite strong sweating and shortness of breath several times a week (5), competitive sports and exercise several times a week (6). Categories are then combined for the analyses as inactive (0-1), light activity (2), and moderate or vigorous activity (3-6).[128]

There has been a sharp decline in physical activity across the globe with the advancement of technologies (e.g. robotics, elevators) which has caused the physical activity to decrease as a whole.[129] Physical inactivity (lack of physical activity) has been identified as the fourth leading risk factor for global mortality (6% of deaths globally)[130]. Healthy lifestyle and physical activity is known to have a protective effect towards many medical disorders. The risk of developing AD lessens with increased physical activity during midlife. This is shown by majority of studies while a few report no effect. Large prospective cohort studies have been conducted to test the effect and many show delay in AD onset.

Physical activity appears to be one of the main factors that contribute to maintenance of a healthy ageing brain. Recently, positive effects of physical activity have been reported in brain functioning. Growing evidence supports the view that physical activity can slow cognitive decline. Considering this, a delay in the onset of cognitive decline or slowing of disease progression may have significant public health impact.

Epidemiological evidence on physical activity and its association with dementia may be influenced by numerous biases such as marked lifestyle differences between sedentary participants and physically active ones. Potential confounders between physical activity and the risk of AD or dementia exist. Importantly, the assessment of physical activity is questionable in various epidemiological studies. The involvement in physical activity varies during a lifetime and an assessment done once may not correspond to mean long-term activity, and even less to activity over subject's past lifetime. Also, inactivity may be a prodromal symptom of AD rather than cause of cognitive decline.

2.2.2 Intensity

In many longitudinal studies, a standardized physical activity scale measuring intensity and duration of physical activity is generally lacking. Moreover, they are not designed to determine a threshold of physical activity that is protective towards AD. Some studies report that strenuous physical activity is associated with less cognitive decline[131]. On the other hand, employing high intensity physical activities in the elderly can be challenging. Most epidemiological data is inclined towards the opinion that intensity threshold of physical activity is low to have a statistically significant impact on cognitive functioning or dementia prevention[132]. Physical activity such as playing golf, walking 1.6 km per day, playing tennis twice a week, walking 1.5 hours a week at a speed of 21-30 minutes per mile, doing 15 minutes of activity at a time, three times per week, cycling, aerobics, swimming, or other exercise around the year was associated with significantly lower risk of dementia[14,133]

Persistent and moderate level engagement in physical activity showed beneficial effects on psychomotor processing speed and brain activation[134]. Aerobic exercise for one hour thrice a week continued for more than six months was shown to increase brain volume in 60–79 years, community dwelling participants studied by Colcombe and colleagues[135]. However, no dose-response relationship was found between physical activity and prevention of cognitive decline. Another study reported that moderate physical activity less than three times a week and high physical activity three times a week or more to be associated with a reduced

incidence of cognitive impairment after two years in a large population based cohort of old people[136]. This study too did not show a dose-related response between physical activity and incidence of cognitive impairment.

2.2.3 Effects of physical activity on general brain functioning

Significant health benefits can be obtained by including a moderate amount of physical activity. Additional health benefits can be gained through greater amounts of physical activity. It reduces risk of premature mortality in general and of coronary heart disease, hypertension, colon cancer, and diabetes mellitus in particular. Physical activity also improves mental health and is important for muscles, bones, and joints. Underpinning physical activity recommendations is a growing evidence how physical activity affects physiologic function. The body responds to physical activity through expressing its positive effect on musculoskeletal, cardiovascular, respiratory and endocrine systems. Regular participation in physical activity also appears to reduce depression and anxiety, improve mood, and enhance ability to perform daily tasks throughout the life span.[3,14]

Taylor and Faulkner link physical activity to mental health in three dimensions: self-perception, emotional and cognitive functioning[137,138]. Because of complex associations between physical fitness, motor coordination, cognitive and attentional functioning, limited research investigates how physical activity and sports influence cognitive functions[139,140]. The benefits of physical activity for cognitive functioning emerge from chronic and acute exercise research that investigate the long-term effects of habitual participation in physical activity and the short-term effects of single bouts of exercise on cognition, respectively.

Physical activity has cogent reasons to be offered as an effective mental health promotion strategy. Initially, it is potentially cost effective as an intervention or for participation. Pharmacologically, it is associated with minimal adverse side effects as compared to drug-based interventions.

2.2.4 Physical activity and risk of AD

One possible mechanism is as alteration in cerebral vascular function and brain perfusion. Animal studies have shown that physical activity can stimulate angiogenesis, brain perfusion and neurovascular integrity within 3 to 4 weeks. Another possible mechanism is environment enrichment associated with greater physical activity. Basic research has shown that enriched environments are activity prone and contribute to enhanced brain plasticity via synaptogenesis, neurogenesis and attenuation of neural responses to stress. Other

experimental studies have shown more astrocytes and neuroblasts with proliferative ability in the hippocampal area and increased number of neurons in transient stage[141]. Also, neurogenesis in wheel-running mice was mediated by N-methyl-D-aspartate receptors, a shift in corticoid receptor expression in the hippocampus, and activation of insulin like growth factor 1, vascular endothelial growth factor, brain derived neurotropic factor, and endorphins[142].

Physical activity is also associated with increased blood perfusion of brain regions that modulate attention in humans. Colcombe et al [143] found that aerobic exercise in older adults significantly improves task-related activity in attention control areas. It is suggested that the increased activity was due to physical activity stimulated synaptogenesis, increased blood supply, and unspecified cholinergic effects.

An acute bout of physical exercise induces transitory behavioral and psychological changes which reflect a transient modulation of the activity of neural networks. Specifically, acute physical exercise is hypothesized to produce transient changes in arousal level and in cognitive processes that are responsible for mental resource allocation. The effects of acute exercise have been primarily studied in physically fit adult populations. According to Yoshitake et al[144], regular physical activity may sustain cerebral circulation by decreasing blood pressure reducing plasma lipid levels, and inhibiting platelet aggregability, thereby preserving cognitive functions.[145]

Significantly lower Aβ plaque levels in the frontal cortex and hippocampus of transgenic mice were observed after 5 months of voluntary exercise[146]. Studies in humans reported low levels of exercise in individuals with higher levels of Aβ studied by Pittsburgh compound B (PiB) positron emission tomography[147].

In AD, level of many neurotransmitters like acetylcholine are known to be lower. Up to 70% norepinephrine projecting cells are lost in AD. Various studies have shown that exercise induces several neurotransmitters, including serotonin, acetylcholine, dopamine, epinephrine and norepinephrine[148,149]. Peripheral levels of catecholamines (dopamine, epinephrine and norepinephrine) increase in human subjects immediately after exercise[150]. Increases in dopamine and epinephrine levels was found to be positively associated with better immediate (dopamine) and long-term (epinephrine) retention when tested on a vocabulary task. Moreover, the activity of receptor neurotransmitter subtypes which can change cortical activity has been shown to increase with exercise[151].

In voluntary wheel running mice, twice the amount of surviving new born cells in the adult dentate gyrus suggest that aerobic exercise alone is sufficient to significantly increase neurogenesis level[152,153]. Increased levels of hippocampal synaptic plasticity in mice completing voluntary wheel running regimen was observed [153,154]. Physical activity is known to up regulate endothelial nitric oxide synthase leading to improvement in cerebral blood flow and greater levels of angiogenesis[155,156].It has been suggested that exercise might reduce the risk of AD by lowering age-associated chronic inflammation[157]. Physical activity is a protective factor for Type 2 diabetes and is known to enhance insulin sensitivity; Leisure time physical activity is inversely associated to insulin levels. It thus can be projected that there is a potential link between AD and physical activity since insulin sensitivity and metabolic disease have been implicated in AD and are associated with alteration in Aβ processing[158].

2.2.5 Physical activity in people with AD

In AD patients, falls, malnutrition, behavioral disturbances or depression are frequent and severe consequences of disease. These complications result in a high rate of functional decline and their prevention may improve the course of dementia, quality of life and reduce the burden on care givers.

Physical activity improves bowel movements, appetite, sleep, agitation, mood, balance, gait and strength. These effects tend to end up in better cognitive functioning. An acute bout of physical exercise induces transitory behavioral and psychological changes which reflect a transient modulation of the activity of neural networks. Specifically, acute physical exercise is hypothesized to produce transient changes in arousal level and in cognitive processes that are responsible for mental resource allocation. The effects of current exercise have been primarily studied in physically fit adult populations[159,160].

In frail AD patients residing in nursing homes, physical activity improves function[161,162]. It specifically yields potential protective factor countering functional decline and accompanying complications such as falls, fractures, malnutrition and behavioral disturbances such as depression and anxiety. Physical activity is known not just to prevent key problems in demented patients but also impacts burden of disease and improves quality of life[163,164]. Thus, apart from managing the complications of AD, physical activity may be a realistic approach to delaying cognitive decline.

3 AIMS AND METHODS

3.1 Background

Physical activity has cogent reasons to be offered as an effective mental health promotion strategy. It can be indefinitely sustained by the individual for longer periods. It is potentially cost effective as an intervention or for participation. Drugs and non-drug therapies such as cognitive behavioral therapy are expensive and relatively inaccessible or unavailable whereas some patients report a reluctance to take medication. Pharmacologically, physical activity is associated with minimal adverse side effects. It is self-done and does not necessarily involve assistance. Physical activity is known to provide general health benefits which are not stipulated by other therapies. [165,166]

3.2 Aims

3.2.1 General Objective

To conduct systematic review of original research articles assessing association between physical activity and Alzheimer's disease (AD).

3.2.2 Specific Objectives

Whether physical activity has protective effect towards developing AD.

What type, duration and intensity of physical activity is protective towards AD.

What is the quality of the current evidence on physical activity and AD association.

3.3 Methods

The current systematic review was limited to prospective observational and intervention studies.

Criteria for inclusion

Study design: Longitudinal study

Population: Individuals without AD at baseline.

Exposure: Studies which provide a definition for physical activity.

Outcome: Incident early onset or late-onset AD.

Search methods: Medline was searched via PubMed by using the key words dementia, cognitive impairment, Alzheimer's disease, physical activity and exercise. Details of the search strategy are presented in Table 1.

Table 1. MEDLINE search strategy PubMed March 2014 (run on date 23.03.2014)

1) exercise OR "physical activity"
2) Alzheimer's OR "cognitive impairment" OR dementia
3) (((exercise OR "physical activity"))) AND ((Alzheimer's OR "cognitive impairment" OR dementia))
4) randomized controlled trial[pt]
5) cohort study[mh]
6) follow up study[mh]
7) controlled clinical trial[mh]
8) (#4 OR #5 OR #6 OR #7)
9) (#3 AND #8)

3.3.1 Systematic evaluation of original studies

1) Design, settings and study population
2) Exposure synthesis:
    a) Definition of physical activity
    b) Assessment methods of physical activity
    c) Physical activity assessment period
    d) Frequency, duration and intensity of physical activity
3) Outcome synthesis
4) Quality of studies:
    a) Population representativeness
    b) Assessment of exposure
    c) Outcome assessment
    d) Length of follow-up
    e) Loss of follow-up/drop out
    f) Quality of evidence

Systematic evaluation of studies

1) **Design, setting and study population**

Studies were classified regionally taking into account their study design, setting and study population.

2) **Exposure synthesis:**

a) **Definition of physical activity:** Physical activity mentioned in each study was categorized according to type.

b) **Assessment methods of physical activity:** Studies which assessed physical activity via

- validated questionnaires
- objective and subjective measures
- one question (self-report)

c) **Physical activity assessment period:** Studies were categorized on the basis of physical assessment period as

- whole lifetime
- one year period
- one month or less

d) **Frequency, duration and intensity of physical activity:** The studies were grouped together on the basis of the dynamics of their measurement of physical activity as follows:

- duration, frequency and intensity
- type, duration and intensity
- frequency and duration (translated into intensity according to the type of physical activity)
- duration and activity counts.
- duration and calculating intensity
- frequency and intensity
- duration of physical activity and categorized responses into intensity levels

- duration and frequency
- frequency
- distances walked

Exercise intensity is how hard one exercises or refers to how much energy is expended when exercising. It is the amount of physical power (expressed as a percentage of the maximal oxygen consumption VO2 max) that the body uses when performing an activity. This term is most often used to describe aerobic activity. Aerobic exercise is physical exercise of low to high intensity that depends primarily on the aerobic energy-generating process. Exercise intensity takes into account the duration and expenditure of energy in metabolic equivalents (METs).[167]

3) Outcome synthesis

Studies using the same diagnostic tests and criteria for the diagnosis of AD were grouped together.

4) Quality assessment of included studies

A quality criterion was formed for assessing the risk of bias of the studies included in the review. Since not many validated tools are available to assess the quality of observational studies the validated methods of Shamliyan et al[168-170] were tailored to form the quality criteria based on the prioritization of domains required for the quality assessment of studies in this review. The quality of the studies was reviewed in the following domains:

a) **Population Representativeness:** If both, the age of the study population was <65 years at the beginning of study and the sample size was > 1000 the study population was defined as representative; this definition in the risk of bias assessment table was quoted as "REPRESENTATIVE". If either the population was 65-74 years or the sample size was < 1000 but > 500 the representativeness of the study sample was "MODERATELY REPRESENTATIVE". If the age of the study population was ≥75 years, or the sample size was < 500, defined as non-representative and it was quoted in the risk of bias assessment table as "NOT REPRESENTATIVE". The limitations for age were defined because the prevalence of AD at the age 65 years is 2-3% and it doubles every five years after

the age of 65 years[14]. Also, the disease starts long before it is possible to diagnose clinically, so it is not appreciated to study an older cohort for a short time. Sample sizes for cohort studies depend upon the rate of the outcome, not the prevalence of exposure. Larger sample sizes are required in the cohort studies because the rate of outcome is usually smaller than the prevalence of the exposure, cohort studies typically require larger sample sizes to have the same power as a case-control study.[171]

b) **Assessment of Exposure:** If the physical activity was assessed by using both subjective and objective measures, the assessment of exposure was "GOOD". The physical activity if measured by only subjective measures but through a validated questionnaire or items adopted from a validated questionnaire, this assessment measure was defined as "MODERATE". If the physical activity was measured by only self-report through questions such as "do you exercise regularly? yes/no" or other questions like these without considering validated questionnaires or a specific defined standard for physical activity; such measures were defined as "LOW" in quality.

c) **Outcome assessment:** The studies which in their diagnosis included a step-wise procedure of diagnosis of dementia first and then AD supplemented by other examinations and evidences were considered having a valid outcome assessment. Following elements constituted procedural diagnosis or a valid outcome assessment: A thorough neurological examination, laboratory findings, MRI or CT scan, a consensus panel consisting of neurologist/ additional physicians with expertise in dementia, criteria for dementia based on the Diagnostic and Statistical Manual of Mental Disorders (Third Edition Revised, DSM III-R) / (Fourth Edition, DSM IV)[9], and the diagnosis of Alzheimer disease based on the research criteria established by the National Institute of Neurological Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA)[10]. The studies which used DSM III-R/DSM IV criteria or NINCDS-ADRDA criteria, even if they lacked any other procedures mentioned above were considered having valid outcome assessment. The studies which included neither DSM III-R/DSM IV criteria nor NINCDS-ADRDA were considered having no valid outcome assessment.

d) **Length of follow up:** The length of follow up in regard to age of the participants is an important consideration since the ideal follow up in this case would be

starting at mid-life or the third decade of life till death or at least 14 years or longer when people reach the age of 85 years. The follow up period with reference to the age of participants in each study was defined in terms of quality as follows: follow up of >14 years in participants of age <65 years is considered "GOOD" quality; 6-14 years of follow up in participants of age 65-75 years is "MODERATE" quality; <6 years of follow up in participants of age >75 years is "LOW" quality.

e) **Loss of follow-up/ Drop out:** If the follow-up is started late, then there are participants in the study who already have pre-AD and the follow up may miss out many cases. In this case, there must be those subjects who are at the biggest risk of AD. Hence, the disease might be underestimated and recruitment of participants be subject to selection bias. Each study cohort was checked for loss of participants in (non-response) of <20% out of the analyzed sample, it was considered "GOOD" quality; a loss of participants between 20% to 40% was considered "MODERATE" quality whereas a loss >40% up to half of the study population was considered "LOW" quality. The reasons for dropout/non-response not given/different led to a judgment of low quality of study. 60% attrition rate over 20 years was not much where as 30% attrition rate over a period of 5 years was considered large.

f) **Quality of evidence:** For the overall assessment of the risk of bias per study, the sample representation including the sample size of the study and age of the participants, the assessment method of physical activity and the length of follow up had the most relevant impact on the result of the study and thus the quality of evidence. Representativeness of sample, method of exposure assessment, length of follow up taken into consideration may affect more significantly the reliability of a study in the context of the current review than, for example, drop out. Therefore, the domains were placed into two hierarchical groups. Major domains of bias: (i) population representativeness (ii) exposure assessment, (iii) length of follow up. Minor domains of bias included: (i) outcome assessment (ii) drop-out or attrition. The study-level risk of bias was rated as: Good (low risk in all major domains and ≥1 of the minor domains), moderate (low risk of bias in ≥2 major and 2 minor domains), or low (low risk of bias in <2 major domains).

4 RESULTS

The specific search strategy retrieved 441 results. Going through the titles of the articles, 125 articles were selected and their abstracts were reviewed. Full texts for certain studies were checked if the abstract seemed promising; and then out of 125 results, 18 potential studies were chosen. The reference lists of the potential studies were hand-searched to counter check if any potential study was not captured by the search strategy. Reviews, case reports, cross-sectional studies and non-English studies were excluded.

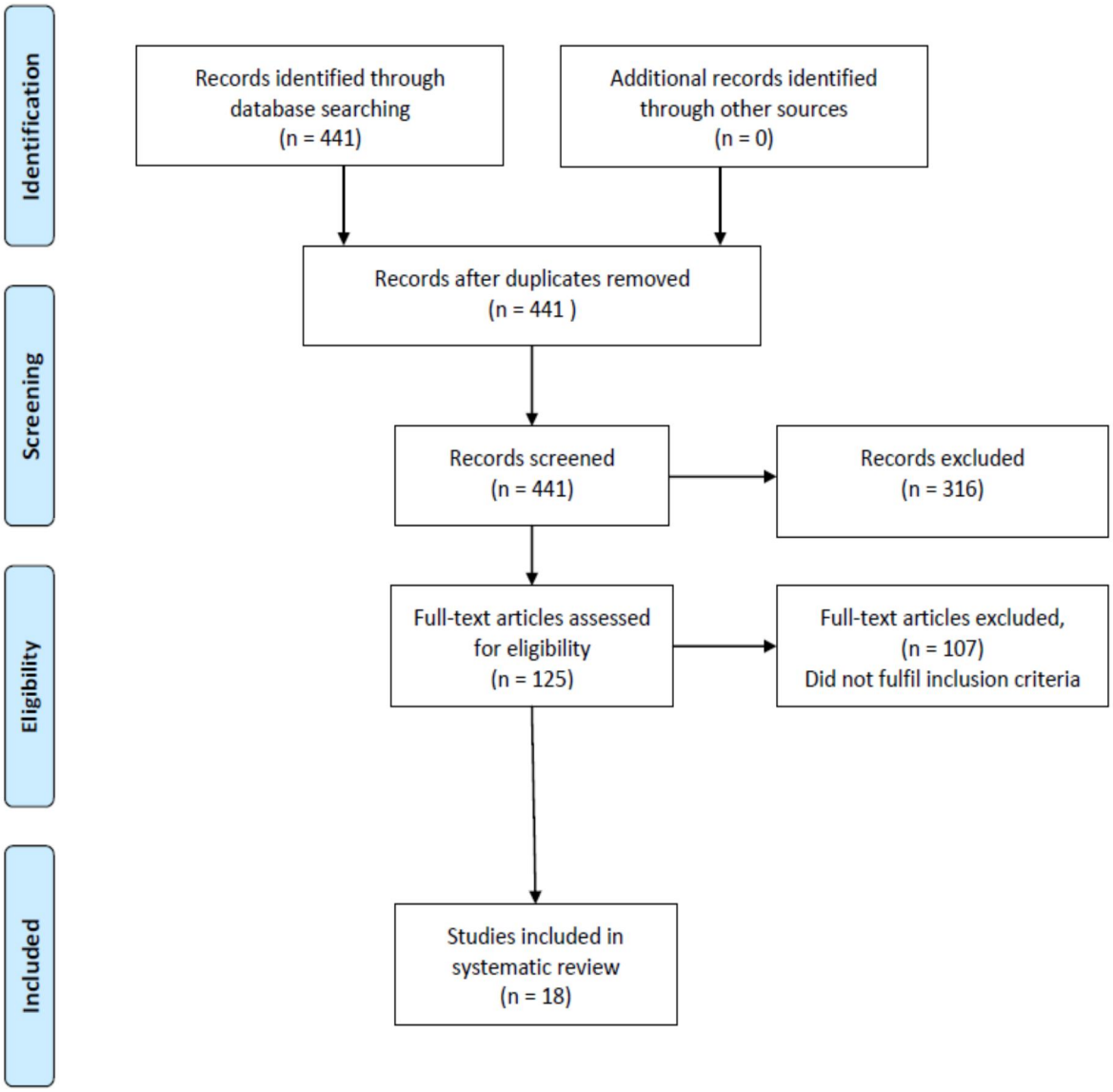


Figure 2. Search Results

Table 2: Studies included in the systematic review

Study	Design and setting	Study population	Mean follow up (years)	Assessment of physical activity	Association between physical activity and AD
Renee 2013[172]	Cohort, P.B Netherlands	4406, 72.7 years	8.8	Questionnaire	Inverse association
Buchman 2012[173]	Cohort, C.D Illinois, U.S.	716, 81.6 years	4	Subjective & Objective	Inverse association
Verdelho 2012[174]	Cohort,(LADIS), P.B Europe	638, 65-84 years	3	Questionnaire	Inverse association
Scarmeas 2009[175]	Cohort, C.D Manhattan, U.S	1880, ≥ 65 years	5.4	Questionnaire	Inverse association
Taaffe 2008[176]	Cohort, P.B Honolulu, Hawaii	2263, 71-92 years Men only	6	Questionnaire	Inverse association
Larson 2006[177]	Cohort, P.B Seattle, U.S.	1740, ≥65 years	6.2	Questionnaire	Inverse association
Podewills 2005[178]	Cohort, C.D U.S.	3375, ≥65 years	5.4	Questionnaire	Inverse association in APOE 4 carriers
Rovio 2005[179]	Cohort, P.B Finland	1239, 39-64 years	21	Questionnaire	Inverse association
Abbott 2004[180]	Cohort, P.B Honolulu, Hawaii	2257, 71-93 years Men only	8	Questionnaire	Inverse association
Lindsay 2002[181]	Cohort, P.B Canada	4615, ≥65 years	5	Self-report	Inverse association

Table 2 continued

Study	Design & Setting	Study Population	Mean follow up (years)	Assessment of Physical activity	Association between Physical activity and AD
Verghese 2003[182]	Cohort, C.D New York, U.S.	469, 75-85 years	21	Questionnaire	Dancing was the only PA to protect against dementia
Laurin 2001[183]	Cohort, C.D Canada	4615, ≥65 years	5	Questionnaire	Inverse association
Scarmeas 2001[184]	Cohort, C.D New York, U.S	1772, ≥ 65 years	7	Questionnaire	Inverse association
Yoshitake 1995[144]	Cohort, C.D Japan	828, ≥65 years	7	Questionnaire	Inverse association
Ravaglia 2008[185]	Cohort, P.B Italy	749, ≥65 years	3.9	Questionnaire	No significant association
Rovio 2007[186]	Cohort, P.B Finland	1158, 39-64 years	20.9	Questionnaire	No association
Ymada 2003[187]	Cohort P.B, Japan	1774, 30-70 years	30	Questionnaire	No association
Wilson 2002[188]	Cohort , C.D Chicago, U.S.	835, ≥65 years	4.1	Questionnaire	No association

AD, Alzheimer's Disease; PA, Physical Activity; C.D, Community dwelling; P.B, Population based

18 selected studies met the inclusion criteria which were systematically reviewed by the following order:

4.1 Design, setting and study population

All eighteen studies were longitudinal observational studies (Table 2).Of these eighteen studies, ten studies were population based studies and the remaining eight were conducted in community dwelling persons. Seven studies were conducted in the U.S [173,178,182,184,188]. Five studies were from Europe [172,174,179,185,186]. Four studies were from West Pacific/ Asia [144,176,180,187]. Two studies were from Canada [181,183].

Of the five European cohorts, two studies were conducted in Finland on population aged 39-64 years old, at the time of physical activity assessment. Among cohort of 1449 subjects the effect of leisure time physical activity [179] and the effect of work-related physical activity were explored.[186] One Italian cohort consisted of 749 subjects aged ≥ 65 years.[185] LADIS cohort had 638 multi-national participants aged 65-84 years from 11 European centers [174]. One study cohort from Netherlands consisted of 4406 subjects with mean age 72.7 years [172].

Out of seven studies from the U.S., six had participants aged ≥ 65 years [173,175,182,184,188] only the study of Verghese et al [182], had older population 75-80 years old participants. Amongst the four studies from Western Pacific, Abbott et al [180] and Taaffe et al [176] studied a Hawaiian cohort with participants 71-92/93 years of age, whereas Ymada et al[187] studied 30-70 year-old Japanese population. Yoshitake et al [144] had Japanese cohort with 828 participants ≥ 65 years of age.

Of the eighteen studies, one study had a sample size less than 500 [182]. Five studies had sample size greater than 500 but less than 1000[144,173,174,185,188]. Two studies had sample size more than 1000 and less than 1500 [179,186]. Four studies had sample size between 1500 and 2000[177,184,187]. Two studies had sample size greater than 2000 and less than 2500 [176,180]. One study had sample size of 3660 participants [178]. Three studies had sample size greater than 4000; one study had 4406 participants [172] and two studies had 4615 participants [181,183].

Sixteen studies had both genders amongst the participants. Two studies[176,180] were conducted among men only.

4.2 Exposure Synthesis

4.2.1 Definition of physical activity

Nine studies assessed only leisure time physical activity [174,175,177,179,181-184,188]. Two studies assessed both work-related and leisure activities [144,187]. Two studies assessed household activities and leisure time physical activity[172,178]. One study assessed only work-related physical activity.[186] One study assessed work-related, household and leisure time physical activity [185]. One study assessed only walking per day as physical activity [180]. Two studies assessed 24-hour activity [173,176]. Physical activity definition, types, measurements are summarized in Table 3*: Physical activity assessment of studies*.

4.2.1.1 Type of Physical Activities:

Leisure Physical Activity:

The studies using physical activity questionnaires included the following leisure-time activities:

playing tennis[175], golf[175,178,182,188], bicycling[172,173,175,177,178,182,188], dancing[175,178,182,188] (ballroom dancing)[182,185] (aerobic dancing)[175], participating in group exercises[182], playing team games such as bowling[175,178,182,188], walking[172,175,177], walking for exercise,[182,184,188] hiking[175,177,178], aerobics or calisthenics[173,175,177,178,188], swimming[173,175,177,178,182,188], water aerobics[177], exercise in water[173,178,188], weight training or stretching[177], physical conditioning [184] other exercise[177], general exercise,[173,178,188], regular exercise [181,183], leisure time physical activity [179], jogging[175] or running [178,188], playing handball[175], horseback riding[175], other diverse sports or other hobbies [172,184].

Household physical activity:

The household activities were defined as gardening[172,175,176] or yard work[173,178,188] climbing more than two flights of stairs[182], doing housework[182], babysitting[182] carpentry[176], lifting or shoveling [176].

Work-related physical activity:

The intensity of work-related physical activity and duration and type of commuting to work was assessed via questionnaire in two studies.[144,186]

4.2.2 Assessment methods of physical activity:

One study assessed physical activity both subjectively and objectively [173]. Seventeen studies used subjective measures of assessing physical activity through questionnaires[144,172,174-180,182-188] or self-report.[181]

Objective and subjective measures: Objective assessment of physical activity is employed through techniques such as heart rate monitoring, actigraphy, step-counter, etc. Using both subjective and objective measures reduces the information bias and increases the validity and reliability of the results. Buchman et al used both objective (actigraphy) and subjective measures (questionnaire) to assess physical activity [173].

Questionnaires: Paffenbarger Physical Activity Questionnaire (PPAQ) was used by Ravaglia et al [185]. The participants were asked 1) how many city blocks (or the equivalent: 12 block _ 1 mile) they walked each day for exercise or as a part of their normal routine and about their usual outdoor walking pace; 2) how many flights of stairs they climbed each day; 3) about frequency and duration of their participation per week during the past year in any other occupational, recreational, or sport activity. Physical activity index from the PPAQ is a moderately good tool for measuring habitual physical activity status and it has acceptable short-term repeatability. Podewills et al used a modified Minnesota Leisure Time Activity Questionnaire asking participants about the frequency and duration of 15 different types of activities over the previous two weeks [178].

Verdelho et al interviewed participants based on the recommendations of American Heart Association Scientific Position (at least 30 minutes of activity on at least 3 days per week) [174]. The study of Ymada and colleagues used the physical activity questionnaire from the Framingham Study [187].

Buchman et al used both subjective and objective measures of physical activity assessment; self-report by the subjects for the assessment of late-life physical activity was based on questions adapted from the 1985 National Health Interview Survey[173] whereas Wilson et al used the 1985 National Health Interview Survey adapted for use with older persons. Two slightly different versions of the Godin leisure time exercise questionnaire[189] were used by Scarmeas and colleagues in their study[175]. The validated Zutphen Physical Activity Questionnaire[190] was used by the Renee et al[172] in their study. In addition to the activities included in the questionnaire, they additionally asked about the household activities. Taaffe et al [176]assessed 24-hour physical activity based on questions regarding the average number of

hours per day spent in five levels of activities, similar to that used in the Framingham[191] and Puerto Rico heart[192] studies. The other eight studies made their own questionnaires [144,179,180,183,184,186,187].

Self-report: Lindsay et al[181] only used a rough measure in their study asking the participants whether they exercise regularly. This measure is loose, since it is not only subject to information bias but also practical recommendations cannot be drawn from such a study. However, the main objective of study was assessing various risk factors for dementia of which one was the level of physical activity. So was the study of Scarmeas et al[184] who asked the participants whether they walk for pleasure or excursion along with other questions about cognitive and social activity.

4.2.3 Physical activity assessment period:

The studies were also reviewed in regard to the length of physical activity assessment period.

Life time: The only study that retrospectively assessed the physical activity during the lifetime was of Rovio et al[186].Weekly leisure-time physical activity and the main occupation during life were assessed.

One year period: The study of Ravaglia and colleagues[185] assessed frequency and duration of the subjects participation per week during the past year in any occupational, recreational, or sport activity. Also, in the study of Larson et al[177] physical exercise was assessed at baseline by asking participants the number of days per week they did each of the certain physical activities for at least 15 minutes at a time during the past year.

One month or less: Scarmeas et al [175]divided the study participants into two subsets. One subset was queried regarding the number of hours during the most recent month in which they engaged in their typical number of activities. The other subset of participants was interviewed regarding recent two week period in which they were engaged in a typical number of activities. Renee et al[172] assessed the physical activity via recall over past two weeks. Scarmeas et al[184] assessed the leisure activities over the past month.). Wilson et al[188] asked persons if they had participated in the activity in the past 2 weeks and if so the number of times and average duration in minutes. Buchman et al [173]used objective measures based on actigraphs worn on the non- dominant wrist measured total daily exercise and non-exercise physical activity was measured 24 hours/day for up to 10 days**.** Abbott et al[180] asked the participants about the walking distance in miles each day.

Verdelho et al[182] assessed physical activity via interview and defined it according to the American Heart Association Scientific Position (at least 30 minutes of activity on at least 3 days per week.

Rovio et al [179] questioned the participants about daily to weekly to monthly to yearly duration and intensity of physical activity. Subjects were dichotomized into ”active” as those participating in leisure time physical activity at least twice a week; ”sedentary” were defined as those who participated in leisure time physical activity less than twice a week. Verghese et al[182] checked the recall period by measuring the frequency of participation over the time period: “daily,” to “several days per week,” to “once weekly,” to “monthly,” to “occasionally,” to “never”. Activities days per week were calculated by responses.

4.2.4 Duration, frequency and intensity

Three studies assessed duration, frequency and intensity of physical activity via questionnaire. [144,179,186] Ymada et al collected information via questionnaire about type, duration and intensity of physical activity [187]. Three studies measured frequency and duration of physical activity which later was translated into intensity according to the type of physical activity performed [175,178,185]. Buchman et al [173] measured duration through questionnaire and activity counts via actigraph and calculated intensity. Renee et al[172] measured duration and calculated intensity. Frequency and intensity was measured by Laurin and colleagues[183] in their study. Taaffe et al [176] assessed duration of physical activity in terms of hours spent in a day and categorized responses into intensity levels. Three studies measured duration and frequency [174,177,188]. Verghese et al[182] measured frequency. Abbott and colleagues[180] in their study calculated walking distance in miles per day. Lindsay et al [181] asked the participants whether they engaged in regular exercise (yes/no), but “regular” was not explicitly defined. Scarmeas et al [184] assessed physical activity by asking the participants if they walked for pleasure or excursion along with other questions about cognitive and social activity. One point was given for participation in each activity.

Four studies evaluated the intensity of physical activity in terms of METS [172,175,178,185]. A Metabolic Equivalent of Task (MET) is defined as the resting metabolic rate, that is, the amount of oxygen consumed at rest, sitting quietly in a chair, approximately 3.5 ml O_2/kg/min (1.2 kcal min for a 70-kg person). As such, work at 2 METS requires twice the resting metabolism or 7.0 ml O_2,/kg/min and three METS requires three times the resting metabolism (10.5 ml O_2/kg/min), and so on. The energy cost of an activity can be determined

by dividing the relative oxygen cost of the activity (ml/kg/min) x by 3.5. [193] The Compendium of physical activities lists activities as multiples of the resting MET level and range from 0.9 (sleeping) to 18 METs (running at 10.9 miles per hour)[194].

Ravaglia et al[185] calculated energy expenditure per week in walking (from 2.5 to 4.5 METs according to pace), stair climbing (8 METs), any other moderate (3 to 6 METs) or vigorous (>6 METs) activity, and total physical activity (sum of energy expenditure in all the previously listed physical activities). Taking a product of frequency, duration and a coefficient, a summary score corresponding to METS was calculated. Participants were then categorized according to this score. Renee et al[172] calculated the intensity by multiplying the MET-value by time spent on a specific activity (in hours) per week by an individual and thus calculated MET-hours. Scarmeas and colleagues[175] considered vigorous activities corresponding to 9 METs, moderate activities to 5 METs, and light activities to 3 METs.

Laurin et al[183] classified the intensity of physical activity as high, moderate and low intensity physical activity with walking as reference. They calculated frequency and the intensity by summing answers to the frequency question (≥3 times per week, weekly, or less than weekly) and the intensity question (more vigorous, equal to, or less vigorous than walking). A high level of physical activity corresponded to an exercise engaged 3 or more times per week at intensity greater than walking, while a moderate level of physical activity corresponded to exercise also engaged 3 or more times per week, but of intensity equal to walking. All other combinations of frequency and intensity were considered as a low level of physical activity.

Podewills et al[178], according to intensity and leisure-time energy expenditure (kilocalories/week) assigned METs to each activity and estimated energy expenditure for each person. They expressed the energy expenditure as kilocalories per week in leisure activities.

The study of Buchman and colleagues[173] used measures of intensity as activity counts/hour/day. As a surrogate for aerobic activity, the intensity of daily activity was calculated by dividing the total daily physical activity counts by the total hours/day of all nonzero epochs to yield the intensity of daily physical activity (activity counts/hour/day). Intensity of daily physical activity ranged from 0.04 $x10^5$ counts/hour/day to 0.71 x 10^5 counts/hour/day as recorded by the actigraph.

Taffe and colleagues[176] defined intensity in terms of activity levels being basal (sleeping or lying down), sedentary (e.g., sitting or standing, reading, eating), slight (e.g., walking on

level ground), moderate (e.g., gardening or carpentry), and heavy (e.g., lifting or shoveling). A weighting factor based on the approximate oxygen consumption required for each level of activity was multiplied by the hours spent in that activity and summed across the five levels to derive an index of physical activity. The weighting factors were: 1.0 for basal, 1.1 for sedentary, 1.5 for slight, 2.4 for moderate, and 5.0 for heavy activity. These were categorized into low, moderate and high levels of physical activity.

Yoshitake et al[144] mentioned intensity but did not report the details. They defined the physically active group as those including daily exercise during the leisure period or moderate to severe physical activity at work. They divided the ADL into six categories and defined poor ADL from needing assistance when going out of the home to being bedridden.

Physical activity index was expressed as hours per week by two studies [180,188]. Verghese et al [182] expressed physical activity index as activity days/week. Ymada et al [187] calculated number of hours spent in each activity and oxygen level consumed at each activity.

Abbott et al[180] measured only distance of walking with no mention of intensity. Scarmeas and colleagues [184] relied on a number of self-reported leisure activities. Physical activity was one of the leisure activities and its intensity was not assessed. Likewise, Lindsay et al [181] used self-report measures of physical activity and did not assess intensity.

4.2.5 How the information on physical activity was applied in the analyses: Dichotomization

Rovio et al [186] dichotomized the responses into “active” versus “sedentary”. Those people were defined “active” as who participated in leisure-time physical activity at least twice a week and “sedentary” people were defined as those who participated in leisure-time physical activity less than twice a week. Verdelho and colleagues[174] dichotomized responses into “physically active” versus “physically inactive” based on the question of activity at least 30 minutes and at least 3 days per week. Lindsay et al[181] did dichotomization on the basis of self-report (yes/no) asking the participants if they did regular exercise or not. Larson et al[177] made their analysis on the basis of participants who exercised fewer than three times per week and participants who exercised three or more times per week. In the analysis, frequency of physical activity was categorized as “frequent” if the subject participated at least several times per week and as “rare” if the subject participated once per week or less frequently.

Categorization on the basis of intensity levels of physical activity: Four studies used categorical variables to classify levels of physical activity on the basis of intensity.[176,178,183,185] Scarmeas et al [175] divided responses into no PA, some PA and much PA. Abbott divided participants into quartiles on the basis of distance walked (miles per day). Yoshitake et al[144] assessed physical activity (four categories each for leisure and for work).

Table 3: Physical activity assessment of studies

Study	Age at PA Assessment		Definition of PA		Type of PA				Frequency	Duration	Intensity
	Mid Life	Late Life	Subjective	Objective	Occupational	Leisure	Household	ADL			
Renee 2013[172]		x	x			x	x			x	
Buchman 2012[173]		x	x	x		x	x			x	
Verdelho 2012[174]		x	x						x	x	
Scarmeas 2009[175]		x	x		x	x	x		x	x	
Taaffe 2008[176]		x	x				x			x	
Larson 2006[177]		x	x			x			x	x	
Podewills 2005[178]		x	x			x	x		x	x	

Table 3 continued

Study	Age at PA Assessment		Definition of PA		Type of PA				Frequency	Duration	Intensity
	Mid Life	Late Life	Subjective	Objective	Occupational	Leisure	Household	ADL			
Rovio 2005[179]	x		x			x			x	x	x
Abbott 2004[180]		x	x				x	x	x		
Lindsay 2002[181]		x	x			x			x		
Verghese 2003[182]		x	x			x	x				
Laurin 2001[183]		x	x			x			x		
Scarmeas 2001[184]		x	x			x			x		
Yoshitake 1995[144]		x	x		x	x		x	x	x	

Table 3 continued

Study	Age at PA Assessment		Definition of PA		Type of PA				Frequency	Duration	Intensity
	Mid Life	Late Life	Subjective	Objective	Occupational	Leisure	Household	ADL			
Ravaglia 2008[185]		x	x			x			x	x	
Rovio 2007[186]	x		x		x				x	x	x
Ymada 2003[187]	x		x		x	x	x			x	
Wilson 2002[188]		x	x			x	x		x	x	

PA: Physical activity; ADL: Activities of daily living

4.3 Outcome Synthesis

4.3.1 Diagnosis of AD

A combination of all or few of the following tests was used for the diagnosis of AD by different studies as shown in Table 4. Cognitive Ability Screening Instrument (CASI), which consists of items identical or similar to those used in the Mini-Mental State Examination or Hasegawa's Dementia Scale, was used by four studies. The Informative Questionnaire on Cognitive Decline in the Elderly (IQCODE) completed by the caregiver was used in four studies. Mini-Mental State Examination (MMSE) was performed by seven[144,178-181,183,186] studies along with other diagnostic criteria. None of these seven studies relied on MMSE alone. Of the 18 studies, eight[144,172,175,176,180-182,184] used the criteria from Diagnostic and Statistical Manual of Mental Disorders (Third Edition Revised) (DSM III-R) to conclude the presence or absence of dementia. Of these eight studies, four used both MMSE and DSM III-R[144,172,180,181]. One study used CASI and DSM III-R criteria[180].Criteria from Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM IV)[9] was used for the diagnosis of dementia by seven studies [172,177,179,183,185-187]. Two studies[177,187] used CASI and DSM-IV criteria. The criteria of the National Institute of Neurological Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA)[10] was used by all 18 studies for the judgment of probable or possible AD. Neuroimaging, CT scans and MRI were performed in the respective study or information from the past records was used in ten studies.[144,174-176,180,182,184,185,187,188]

Table 4. Outcome assessment of the studies

Study	Cognitive evaluation	Neuroimaging, laboratory tests for excluding other reasons causing cognitive impairment	Use of accepted diagnostic criteria
Renee 2013[172]	MMSE, GMS	CAMDEX	DSM-III-R, NINCDS-ADRDA
Buchman 2012[173]	Cognitive function tests		NINCDS-ADRDA
Verdelho 2012[174]	Neuropsychological evaluation	MRI	NINCDS-ADRDA
Scarmeas 2009[175]	Neuropsychological evaluation	MRI	DSM-III-R, NINCDS-ADRDA
Taaffe 2008[176]	Proxy interview	CASI, IQCODE, neuroimaging, blood tests, neurological examination	DSM-III-R, NINCDS-ADRDA
Larson 2006[177]	CASI		DSM-IV, NINCDS-ADRDA
Podewills 2005[178]	MMSE	APOE, IQCODE, TICS	NINCDS-ADRDA
Rovio 2005[179]	MMSE	Blood tests	DSM-IV, NINCDS-ADRDA
Abbott 2004[180]	CASI, MMSE	IQCODE, CT, Laboratory findings	DSM-III-R, NINCDS-ADRDA
Lindsay 2002[181]	MMSE,		DSM-III-R, NINCDS-ADRDA
Verghese 2003[182]	Blessed Information Memory Concentration test	CTs, blood tests	DSM-III-R, NINCDS-ADRDA

Table 4 continued

Study	Cognitive evaluation	Neuroimaging, laboratory tests for excluding other reasons causing cognitive impairment	Use of accepted diagnostic criteria
Laurin 2001[183]	MMSE		DSM-IV, NINCDS-ADRDA
Scarmeas 2001[184]	Neuropsychological evaluation	MRI	DSM-III-R, NINCDS-ADRDA
Yoshitake 1995[144]	MMSE, HDS-R	Autopsy, brain CTs, blood tests	DSM-III-R, NINCDS-ADRDA
Ravaglia 2008[185]	MMSE, GDS	CT	DSM-IV, NINCDS-ADRDA
Rovio 2007[186]	MMSE	Blood tests	DSM-IV, NINCDS-ADRDA
Ymada 2003[187]	CASI, IQCODE	MRI	DSM-IV, NINCDS-ADRDA
Wilson 2002[188]	Cognitive function tests	IQCODE, MRI	NINCDS-ADRDA

MMSE, Mini Mental State Examination; HDS, Hasegawa's Dementia Scale; IQCODE, Informative Questionnaire on Cognitive Decline in the Elderly; CASI, Cognitive Ability Screening Instrument; TICS, Telephone Interview for Cognitive Status GMS, Geriatric Mental Schedule; CAMDEX, Cambridge Examination for Mental Disorders in the elderly; CP, Consensus Panel; MRI, Magnetic Resonance Imaging; GDS, Geriatric Depression Scale; CT, Computed Tomography; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders (Third Edition Revised); DSM-IV, Criteria from Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition); NINCDS-ADRDA, National Institute of Neurological Disorders and Stroke and the Alzheimer's disease and Related Disorders Association

Table 5. Risk of bias assessment of the studies including population representatives, quality of exposure assessment, quality of outcome assessment, length of follow up and drop-out rate.

Study	Population	Exposure Assessment	Valid outcome assessment	Length of follow up	Drop-out	Quality of evidence
Studies with inverse association						
Renee 2013[172]	MR	M	Yes	M	M (26%)	M
Buchman 2012[173]	MR	G	Yes	L	L (43%)	L
Verdelho 2012[174]	MR	M	Yes	L	G (9%)	L
Scarmeas 2009[175]	MR	M	Yes	L	L (55%)	L
Taaffe 2008[176]	MR	M	Yes	L	M (39%)	M
Larson 2006[177]	MR	M	Yes	M	M (23%)	M
Podewills 2005[178]	MR	M	Yes	L	G (10%)	M
Rovio 2005[179]	R	M	Yes	G	G (14%)	M
Abbott 2004[180]	MR	M	Yes	M	M (39%)	M
Lindsay 2002[181]	MR	L	Yes	L	L (49%)	L
Verghese 2003[182]	NR	M	Yes	G	G (39%)	M
Laurin 2001[183]	MR	M	Yes	L	L (49%)	L
Scarmeas 2001[184]	MR	M	Yes	M	G (16.6%)	M
Yoshitake 1995[144]	MR	M	Yes	M	G (0.2%)	M

Table 5 continued

Study	Population	Exposure assessment	Valid outcome assessment	Length of follow up	Drop out	Quality of evidence
Studies with non-significant to no association						
Ravaglia 2008[185]	MR	M	Yes	L	L (44%)	L
Rovio 2007[186]	R	M	Yes	G	G (21%)	M
Ymada 2003[187]	R	M	Yes	G	G (28%)	M
Wilson 2002[188]	MR	M	Yes	L	L (67%)	L

Population Representativeness: Age <65 ; Sample size > 1000 = Representative (R)

Age 65-74 years; Sample size < 1000 and > 500 = Moderately Representative (MR)

Age ≥75 years; Sample size < 500 = Not Representative (NR)

Exposure Assessment: Subjective and objective measurement = Good (G);

Subjective measurement (validated questionnaire or items adopted from a validated questionnaire) = Moderate(M); Self-report measurement (no validated questionnaires or a specific defined standard for physical activity = Low (L)

Length of follow up: <6 years = Low (L); 6-14 years = Moderate (M); >14 = Good (G)

Drop-out rate: Loss of participants in (non-response) of <20% = Good (G); loss of participants 20% to 40% = Moderate (M); loss of participants >40% up to half of the study population = Low (L).

Judgment: Major domains of bias: (i) population representativeness (ii) exposure assessment, (iii) length of follow up. Minor domains of bias: (i) outcome assessment (ii) drop-out or attrition. Low risk in all major domains and ≥1 of the minor domains = Good (G); low risk of bias in ≥2 major and 2 minor domains = Moderate (M); low risk of bias in <2 major domains = Low (L).

4.4 Quality of studies

Of the eighteen studies included in the systematic review, fourteen found a significant inverse association between physical activity and AD, nine of these studies formed a moderate quality of evidence whereas five presented low quality evidence (Table 5). One study found trend towards inverse association [185]. Two studies found no association between the two.[187,188] One of the studies found a non-significant trend towards direct association [186]. Among the studies that found non-significant to no association, two studies[186,187] formed moderate quality evidence whereas the other two form low quality evidence[185,188] Hence, there appears to be an inverse significant association between physical activity and AD based on moderate quality evidence available.

Of the eighteen included studies, only three studies had a representative sample with relatively adequate number of middle aged participants.[179,186,187] Rovio et al in both their studies included participants of ages 39-64 years whereas Ymada et al studied the participants aged 30-70 years. Fourteen studies had moderately representative sample whereas one study[182] had a non-representative sample. Others had quite large cohorts with participants as many as 4615.[181] However, in these studies the age of the participants was ≥65 years.

Nearly, all the studies relied on subjective report of physical activity; a few studies measured physical activity through validated questionnaires and thus formed moderate quality physical activity assessment. Only the study of Buchman et al had good measurement of physical activity since they used both objective and subjective assessment measures[173].

The other important consideration in the quality assessment of the studies was a valid outcome assessment. All the eighteen studies had a valid outcome assessment. The diagnostic procedures of certain studies use the recommended criteria of DSM III, DSM III-R, DSM IV[9] or NINCDS-ADRDA[11] only. While other studies assure that the use of the mentioned criteria are well-supported by other evidence such as lab investigations, neuro-imaging, use of neuropsychological batteries to rule out any biased results. This strengthens the quality of the study.

Rovio et al [179,186] and Verghese et al [182] followed up the cohorts for almost 21 years. Ymada et al[187] followed up the study cohort for 30 years. These four studies had a good follow up period. Five studies had a relatively moderate length of follow up period[144,172,177,180,184]. Nine studies had a relatively lower quality based on the length of follow up.[173-176,178,181,183,185,188]

Eight studies had a less drop-outs or losses to follow up rate compared to others and thus were classified as "good". [144,174,178,179,182,184,186,187] Four studies had a moderate drop-out rate.[172,176,177,180] Other six studies had a high drop-out rate and were classified as "low" in the "drop-out" domain of quality assessment[173,175,181,183,185,188].

5 DISCUSSION

5.1 Main Findings: Main association between physical activity and AD

Fourteen studies out of eighteen included studies suggest that there is an inverse association between physical activity and AD based on moderate quality evidence. Of these fourteen studies, nine formed moderate quality evidence, and 5 formed low quality evidence. The 14 studies that found an inverse association between the physical activity and AD assessed the physical activity at age more than 65 years except the study of Rovio et al[179] which measured the physical activity at mid-life. All of these studies had a valid outcome assessment. Of these 14 studies, 13 studies used questionnaires for physical activity assessment whereas only one study used both subjective and objective measures for physical activity assessment. Among these fourteen studies, two studies had the longer follow up [179,182], 6 had a follow up between six to fourteen years [144,172,176,177,180,184], 6 studies had a follow up of less than six years [173-175,178,181,183].

Four studies out of the eighteen included studies found non-significant to no association between physical activity and AD. Among these studies Rovio et al[186] and Ymada et al[187] studied the cohorts at mid-age and followed up the participants for 21 years and 30 years respectively. Both these studies formed moderate quality evidence. The other 2 studies[185,188] had a follow up of less than 5 years. The physical activity assessment of all these studies was subjective. These formed low quality evidence.

5.2 Methodological Considerations

The sample size of the studies included in this review varied from 469 study subjects to 4615 study subjects. Larger sample sizes are required in the cohort studies because the rate of outcome is usually smaller than the prevalence of the exposure, cohort studies typically require larger sample sizes to have the same power as a case-control study.[171] But the age of participants in most studies was ≥ 65 years; age is a crucial confounder because the prevalence of AD doubles every five years after the age of 65 years [14]. As per the study of Abbott et al[180] , walking is associated with reduced risk of dementia independent of cognitive function, suggesting that the risk of dementia could include important factors other than cognition and age.

The physical activity measure must be specific enough to estimate the true effect size, to specify which dimensions of physical activity are of most importance for a particular health outcome, to make cross-cultural comparisons, to monitor temporal trends within populations

and to measure the effect of interventions. The levels of sophistication in measuring physical activity can be ranged in terms of precision from room calorimetry to doubly labeled water to indirect calorimetry to heart rate to movement sensors to self-report whereas the ease of assessment runs backward this course. Some studies used validated questionnaires for measuring physical activity in general population. The reliability of questionnaires is usually good to excellent. In criterion validity a questionnaire is validated against an objective method. Questionnaires provide prevalence estimates of physical activity, the possibility to categorize respondents into activity categories, a poor measure of the absolute time spent at different intensity levels and the associated energy expenditure. In this review, the studies that used validated questionnaires formed a moderate level evidence quality (Table 5). The use of validated questionnaires is preferable rather than self-report which is a loose measure of physical activity assessment. The measurement of physical activity ideally should be done using both subjective and objective measures. Here, the study of Sattler et al [195]is worth-mentioning; they found that objective, skill-related measures of physical fitness served as better predictors of cognitive impairment than health-related objective measures of physical fitness and self-reported measures of physical activity. This may be one explanation why certain studies, including those reviewed here, detected a protective effect of physical activity while others did not. Subjective measures are likely to be biased by social desirability as subjects may tend to report being more physically active than they actually are.

The assessment of lifetime physical activity by retrospective data may be even more biased – especially when considering that episodic memory declines with age and possible changes in physical activity over decades of time. Another possibility why physical activity might not be predictive of cognitive impairment is that the discriminative power of subjective measures is relatively small so that more participants would be needed to detect an effect. Moreover, differences concerning the self-perception of physical activity across countries cannot be completely ruled out. The studies included in the current review were conducted in the developed world with no account of different races, populations across regions and especially those from the developing world.

The approach of measuring physical fitness was adopted by Abbott et al[180] in their study in order to assess the physical capability of the men in their study sample. They assessed walking distances as a function of physical activity and associated it with dementia/AD. These distances were self-reported and hence subject to information bias.

The study of Buchman et al[173] was the only one that used both subjective and true objective measures to assess physical activity. However, this study lacked in quality domains such as representativeness of study participants who were fairly old (81.6 years) and relatively low in number (n<1000). This shows that persons who developed AD in younger age were missed which signifies selection bias. The strength of this study was the use of actigraphy in the community setting to avoid recall bias and to provide an objective measure of both total daily exercise and non-exercise physical activity and determine its association with cognitive decline and incident AD. However, actigraphs used in this study do not differentiate the types of activities that were performed, and removal of the device cannot always be distinguished from periods of no activity.

It is important to note that if the benefits of physical activity are small and cumulative over many years, they may be beyond resolution by a randomized clinical trial which commonly are relatively short in duration. Thus, the field may be forced to draw inferences from well-designed epidemiologic studies.

Many studies followed up an old cohort for a short time like the study of Verdelho et al[174] and others. Yet, there are other studies like those of Rovio et al[179,186], Ymada et al[187] which have followed up middle aged cohorts for a long period. The consideration regarding the length of follow-up is important. Ideally, the follow-up should start at the mid-age and continue till death, long enough to establish a cause and effect relationship and capture all the cases with the incident AD. However, due to practical limitations, this approach is not adopted by many studies. Renee et al found a significant inverse association only with a follow-up up to 4 years and not with a follow-up after 4 years.

This suggests that pre-diagnostic disease during shorter follow-up leading to reverse causality may indeed play a role when assessing physical activity.

5.3 Can practical recommendations be drawn

Arbitrary approaches are used in observational studies to distinguish exercisers from non-exercisers. A relevant measure of intensity and duration or a standardized physical activity assessment scale is generally lacking. These studies have not been designed to determine a threshold of physical activity that starts to protect against cognitive decline or AD. Although some studies have based their cut-off on previous recommendations for health-promoting physical activity, an optimal dose-response effect of regular physical activity can only be suggested from these reports. Whether low-intensity physical activity, such as walking or

high-intensity activity, such as weight bearing can promote brain health stays a practical question. High-intensity activity such as resistance training may be difficult to organize in the community and it is less appealing for sedentary elders in the long term compared to low-intensity aerobic training. Engaging to high-intensity activity may be challenging for frail elderly people.

In order for recommendations on physical activity to be pertinent, they have to be easily adopted by the population. Most data suggest, however, that the intensity threshold of physical activity required for a clinically relevant impact on cognitive decline or dementia prevention is low. Scarmeas et al [184] found that physical activity, mainly assessed on the basis of walking activities, is associated with a reduced risk of dementia. Doing at least 15 minutes of activity at a time, 3 times a week, and per year among the physical activities of walking, hiking, bicycling, aerobics or calisthenics, swimming, water aerobics, weight training or stretching, or other exercise was associated with a significantly lower risk of dementia in the ACT study [177]. In this study, being active (at least 3 activities per week) reduced the AD risk by 32%. Other authors reported significant trends for increased protection with greater intensity of physical activity[196-198]. MET concept of energy intensity represents a simple, practical, and easily understood procedure for expressing the energy cost of physical activities as a multiple of the resting metabolic rate. It provides a convenient method to describe the functional capacity or exercise tolerance of an individual as determined from progressive exercise testing and to define a repertoire of physical activities in which a person may participate safely or gain a prescribed intensity level.

In the Canadian Study of Health and Aging, regular physical activity was associated with lower risk of AD than no activity[183]; an increasing level of physical activity was associated with a decreasing risk of cognitive impairment and dementia in this study. In this cohort, risk of AD was reduced by half in subjects with higher levels of physical activity. These results all suggest that the threshold of intensity that reduces the risk of cognitive decline and dementia is probably low. Previous studies have suggested that moderate activity could reduce dramatically the risk of other chronic diseases such as coronary heart disease. The same appears to be true for brain health. However, the optimal intensity of physical activity required to maximize the slowing of cognitive decline and reduce the risk of dementia remains unclear.

5.3.1 Type of Activity

The benefit of physical activity is related to the amount of activity per day (energy expenditure), rather than to the type and modality of activity according to the American College of Sports Medicine (ACSM) and the Centers for Disease Control and Prevention (CDC)[199]. While some epidemiological studies combine leisure time and occupational physical activity, others investigate the role of physical activity on cognition using a composite score. None of these approaches make it possible to assess the influence of any specific activity on cognition. However, in addition to the increased energy expenditure, some specific physical activities may result in better brain functioning through social interaction and cognitive training. The beneficial effects of social, cognitive, and physical activities on cognitive decline and the prevention of dementia/AD appear to have common pathways [200]. The psychological dimension of physical activity is an important factor. In rodents, voluntary exercises benefit more than forced exercises [201]. In the Cardiovascular Health Cognition Study (CHCS), not total energy expenditure but engagement in various physical activities, was significantly associated with the reduced risk of dementia. People who engaged in 1 or no activity had reduced risk of dementia by half compared to those who engaged in 4 or more different activities[178]. In the Bronx Aging study, dancing was the only specific type of physical activity that significantly reduced the risk of dementia [182]. These results favor the hypothesis that physical activity may affect cognition through its social interactions or cognitive training during the activity. However, other studies also suggested that simple tasks of a physical activity program such as walking prevent cognitive decline[180]. In animal models, physical activity and enriched environment enhance the proliferation of new brain cells and promote brain repair. Leisure activities are mostly cultural and social dependent forms of activities.[4] Also, recall of number of activities may be more reliable than specifics about exercise frequency and duration since it is easier for the participants to recall the type of activity than frequency, duration or intensity.

Podewills et al[178] finding that number of activities has a stronger association with dementia risk than does kilocalorie expenditure may be an artifact of measurement. They used the Minnesota Leisure Time Activity Questionnaire, and its reliability may be lower at low-to-moderate levels of activity [202], levels at which older adults participate. Thus, the number of activities may be a more sensitive indicator at these levels. Furthermore, persons with established physical activity habits may be more precise in their recall than persons who exercise sporadically. It is a challenge to figure out most beneficial types of physical activity since physical activity involves cognitive functions (in addition to energy expenditure and

mobility) that may enhance cognitive performances. Physical, social, and cognitive activities usually overlap. It is thus difficult to ascertain the specific and individual impact of each component on brain functioning.

5.3.2 Frequency, duration and intensity

It is not easy to define what type, frequency, duration and intensity of physical activity is good for brain health. Some studies included in this review assessed physical activity at baseline whereas others assessed subjects' life-long involvement or over the past year. However, the pathophysiological process of AD begins long before cognitive decline is evident and the diagnosis established. Probably, it is necessary to start being physically active in early life. Most authors suggest that the protective effect is not a short-term but a long-term one, such as those reported in cardiovascular or cerebrovascular disease [201]. According to the cognitive reserve hypothesis, physical activity performed across the whole lifespan may contribute to maintain cognitive function in old age[200]. However, results from epidemiological studies also suggest that even in late life, involvement in physical activity is of benefit for brain health.

Most of the results suggest that threshold of intensity reducing the risk of cognitive decline and dementia is probably low. Moderate activity could reduce the risk for other chronic diseases such as coronary heart disease as shown by previous studies holds true for brain health too. However, the optimal intensity of physical activity required to maximize the slowing of cognitive decline and reduce the risk of dementia remains unclear [14].

5.3.3 Other Considerations

Rovio and colleagues[186] assessed work-related physical activity and found it to be associated with increased risk of AD among the persons with low education. . However, they did find a tendency towards a decreased risk of dementia/AD among persons either sedentary or active while commuting to work in both education groups.

Several studies have suggested that ApoE4 may modify the association between physical activity and the risk of dementia. In the CAIDE study, the association between midlife leisure time physical activity and reduced risk of dementia was also more pronounced in APOE4 carriers [179] . Subjects with APOE4 genotype which increases the risk of AD may have less effective neuronal protection mechanisms and may so be more dependent on lifestyle-related factors [179] whereas the association between dementia risk and physical activity was

significant in APOE4 non-carriers but absent in carriers in the Cardiovascular Health Cognition Study [178].

In the Canadian Study of Health and Aging, physical activity was found to have a greater protective effect against dementia in women than in men [183]. Interactions between hormones and physical activity in women have been suggested to explain cognitive vitality in women [203-205]. The levels of brain-derived neurotrophic factor (BDNF), a molecule involved in neurogenesis and neuroprotection are increased by estrogen replacement as well as physical activity. Estrogens and physical activity may have a synergic effect on brain functioning. But, these results may also be related to the smaller number of men studied and so the lower statistical power of these epidemiological analyses.

5.4 Strengths and limitations

In contrast to the previous reviews, [206,207] this review includes more studies. None of the previous reviews was done to systematically review the literature between physical activity and AD only. Besides this, a formal risk of bias assessment for the included studies was performed and incorporated. These assessments in the analysis and conclusions were drawn where none of the other reviews did so.

The quality of the studies is considered extremely important especially in exposure assessments, follow up years and sample selection, which were the major factors in coming to clear conclusions. The current evidence shows protective effect of physical activity on the risk of AD. However, the definition and measurement of physical activity varies from study to study. Some define physical activity in terms of activities of daily living (ADL) or regular exercise while others define it as activities of leisure time or sport activities; the measurements too, may be subjective (questionnaires) or objective measures. This poses a challenge in defining the physical activity that could have a protective effect even regarding the type, duration and intensity. Further, much work yet needs to be done in understanding the mechanisms working behind these associations. Many randomized controlled trials show beneficial impact of physical activity in patients with AD. However, the threshold of impacting physical activity yet needs to be defined.

It is quite challenging to distinguish between the effects of physical activity intrinsically and the effects related to cognitive stimulation during physical activities involving cognitive functions. Moreover, it is difficult to determine specific effects of mobility and energy expenditure on brain functioning.

The findings of this review are not completely conclusive and comprehensive due to limitation of time and human resource. There are studies that the applied search strategy could not capture all the studies for example studies using terms like “occupation”, “principle exercise”, etc. Moreover, only one database was searched and there may exist more literature that remained untapped in this thesis work. All the studies were conducted in the developed countries where the elderly care and other life-style factors are different by and large from those prevalent in the third-world countries. A meta-analysis of the selected studies was not performed because of heterogeneity of exposure assessment methods used by the studies Moreover, only one of the study questions: “Whether physical activity has protective effect towards developing AD” was answerable through a meta-analysis whereas the other two objectives could not be met through it. Bias is expected since this is the work of one author only.

5.5 Recommendations for future research

Current clinical evidence of the benefits of physical activity on the prevention of AD relies on epidemiological studies. These approaches are exposed to many sources of bias. First, in most studies, the reliability of the physical activity assessment is questionable. Assessment relies on one single question; a composite score based on physical activity during leisure and at work, and estimated average energy expenditure. Some research protocols have used validated standardized physical activity scales. The collection of self-reported activities introduces reporting bias. The exact type, frequency, and duration of activity are usually not quantified. Physical activity is assessed at study baseline but this assessment may not correspond to a mean stable regular activity in the long term and even less to activity over the subject’s past lifetime. The time elapsing between physical activity assessment and the onset of dementia or cognitive decline varies. Mean follow-up between physical activity assessment and cognitive assessment varies from 3 to 30 years. Second, one important limitation of these studies is that initial cognitive decline is associated with functional decline. In fact, inactivity may be a manifestation of the early phase of dementia rather than a risk factor. Most epidemiological studies have tried to reduce this potential effect of behavior changes on physical activity in the early phase of AD by excluding subjects with low cognitive function at baseline or those who converted to AD in the early phases of follow-up. However, behavior disturbances such as depression, not assessed at baseline, usually precede AD and result in low physical activity. Third, the mean follow-up is relatively short in case of most of the studies compared with the decade before pathophysiological changes begin to be

symptomatic and enable the diagnosis of dementia to be confirmed. Only one study investigated the long-term association between midlife physical activity and the risk of dementia or AD [179]. Fourth, another main limitation in interpreting these epidemiological studies is that despite adjustment for several potential confounders, sedentary participants differ from exercisers in many ways. There exist numerous other potential confounders that may influence the relationship between exercise and risk of dementia. Fifth, causality must be drawn with caution from observational studies.

Based on the moderate quality of evidence and the difference in effect estimate by study design, there is sufficient evidence for a link between physical activity and AD. That is why a relationship between the two cannot be ruled out. The uncertainty and lack of good quality Studies is largely due to less-than-valid exposure measurement and can only be resolved by means of better data in the future. Studies in non-demented participants with objective and subjective measurements, ideally in cohorts with long, prospective follow-up are needed. Validation studies of interview/questionnaire data are much needed to find out if and, to what extent, recall bias occurs.

6 CONCLUSION

AD is a growing problem with respect to rapidly aging population. Not only it deteriorates life of the patient at individual, family and societal level, it also poses a massive economic challenge to the society. A number of risk factors have been studied in association to AD. Of these, physical activity is one. In this age of rapid advancement of technology, people are reluctant towards physical activity. Therefore, it was thought important to conduct this systematic review to study the preventive role of physical activity as a cost-effective intervention with AD perspective.

Other compilation of literature does not deal specifically with physical activity and AD association, so it was aimed to collect evidence on AD and physical activity association only. The definition of "Physical Activity" varies from study to study. Another objective was to define a threshold for physical activity that could be protective towards AD. Also, meta-analysis and reviews have that been conducted so far, do synthesize the literature to test the association between physical activity and AD or dementia. But the quality of the evidence provided by these studies based on the methodological considerations has not been thoroughly studied. Hence, another aim was to assess the quality of the evidence provided by the studies included in this review.

It was found that the physical activity is protective towards AD. Out of eighteen studies, fourteen favored an inverse association between the two. It is difficult to ascertain what type, duration and intensity of physical activity is protective towards AD since the studies varied largely in their methodologies. The assessment of physical activity in majority of the studies relied upon subjective reporting, different definitions of physical activity, non-uniform measurement methods and criteria and hence the exact type, intensity and duration of physical activity which is beneficial could not be captured.

The major deciding domains for the quality of the studies were population representativeness, exposure assessment and length of follow up. The quality of eleven studies was moderate, and seven studies had low quality. Of the 18 selected studies, 14 found a significant inverse association between physical activity and ADS, 9 of these studies formed a moderate quality of evidence whereas 5 presented low quality evidence. Of 18 studies, 4 studies found non-significant to no association and one study with low quality evidence found a trend towards inverse association. One study with moderate quality evidence found a trend towards direct

association. Two studies with moderate quality evidence found no association between the two.

Future studies need to have better study designs with younger population, objective exposure assessment, longer follow-up starting at mid-age.

7 REFERENCES

1. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: A systematic review and meta-analysis. Alzheimer's Dement. 2013; 9(1):63-75.e2.

2. Qiu C, Kivipelto M, von Strauss E. Epidemiology of Alzheimer's disease: Occurrence, determinants, and strategies toward intervention. Dialogues Clin Neurosci. 2009; 11(2):111-128.

3. Surgeon General U.S. Public Health Service. Physical activity and health. 1996.

4. Black JE, Isaacs KR, Anderson BJ, Alcantara AA, Greenough WT. Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. Proc Natl Acad Sci U S A. 1990; 87(14):5568-5572.

5. Stay physically active. Alzheimer's Association 2014. (Accessed 07.07.2014) http://www.alz.org/we_can_help_stay_physically_active.asp.

6. Alzheimer's disease facts and figures, Alzheimer's & dementia. Alzheimer's Association. 2012; 8(2).

7. Bird TD. Alzheimer disease overview. In book: Pagon RA, (ed.). GeneReviews. Seattle: University of Washington, 1998. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1161/

8. Förstl H, Kurz A. Clinical features of Alzheimer's disease. Eur Arch Psychiatry Clin Neurosci. 1999; 249(6):288-290.

9. American Psychiatric Association, Task force on DSM-IV, ed. Diagnostic and statistical manual of mental disorders: DSM-IV. 4th ed. Washington DC: American Psychiatric Association; 1994.

10. Dubois B, Picard G, Sarazin M. Early detection of Alzheimer's disease: New diagnostic criteria. Dialogues Clin Neurosci. 2009;11(2):135-139.

11. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the national institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement. 2011; 7(3): 263-269.

12. Fillenbaum GG, van Belle G, Morris JC, Mohs RC, Mirra SS, Davis PC, Tariot PN, Silverman JM, Clark CM, Welsh-Bohmer KA, Heyman A. Consortium to establish a registry for Alzheimer's disease (CERAD): The first twenty years. Alzheimer's Dement. 2008; 4(2): 96-109.

13. Li Yun, Luikart B, Birnbaum S, Shari B, Chen J, Kwon C, Kernie S, Bassel-Duby R, Parada L. TrkB regulates hippocampal neurogenesis and governs sensitivity to antidepressive treatment. Neuron. 2008; 59(3): 399-412.

14. Galvin JE. Alzheimer's disease. In book: A. J. Sinclair, J. E. Morley, B. Vellas, (ed.). Pathy's principles and practice of geriatric medicine 2(5). Chichester, UK: John Wiley & Sons, Ltd. 2012.

15. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. Lancet. 2011; 377(9770):1019-1031.

16. Raghavan R, Khin-Nu C, Brown AG, Day KA, Tyrer SP, Ince PG, Perry EK, Perry RH. Gender differences in the phenotypic expression of Alzheimer's disease in Down's syndrome (trisomy 21). Neuroreport. 1994; 5(11):1393-1396.

17. Shi F, Liu B, Zhou Y, Yu C, Jiang T. Hippocampal volume and asymmetry in mild cognitive impairment and Alzheimer's disease: Meta-analyses of MRI studies. Hippocampus. 2009; 19(11):1055-1064.

18. Dhikav V, Anand K. Potential predictors of hippocampal atrophy in Alzheimer's disease. Drugs Aging. 2011; 28(1):1-11.

19. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 1991;82(4):239-259.

20. Brain with Alzheimer's disease. Bright Focus Foundation 2014. (Accessed 04.04.2014). http://www.brightfocus.org/alzheimers/about/understanding/brain-with-alzheimers.html.

21. Zerr I, ed. Epidemiology of Alzheimer's disease, understanding Alzheimer's disease. ISBN: 978-953-51-1009-5 ed. InTech DOI: 10.5772/54398; 2013.

22. Sosa-Ortiz AL, Acosta-Castillo I, Prince MJ. Epidemiology of dementias and Alzheimer's disease. Arch Med Res. 2012; 43(8):600-608.

23. Prince M. Dementia in developing countries. A consensus statement from the 10/66 dementia research group. Int J Geriatr Psychiatry. 2000; 15(1):14-20.

24. Ott A, Slooter AJ, Hofman A, van Harskamp F, Witteman JC, van Broeckhoven C, van Duijin CM, Bretler MM. Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: The Rotterdam study. - The Lancet.1998; 351(9119):1840-3

25. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M, Alzheimer Disease International; Global prevalence of dementia: A Delphi consensus study. Lancet. 2005; 366(9503):2112-2117.

26. Aguero-Torres H, Fratiglioni L, Guo Z, Viitanen M, von Strauss E, Winblad B. Dementia is the major cause of functional dependence in the elderly: 3-year follow-up data from a population-based study. Am J Public Health. 1998; 88(10):1452-1456.

27. Schneider J, Murray J, Banerjee S, Mann A. EUROCARE: A cross-national study of co-resident spouse carers for people with Alzheimer's disease: I--factors associated with carer burden. Int J Geriatr Psychiatry. 1999; 14(8):651-661.

28. Families care: Alzheimer's caregiving in the United States. Alzheimer's Association 2004. (Accessed 02.06. 2014). https://www.alz.org/national/documents/report_familiescare.pdf

29. Alzheimer's facts and figures. Alzheimer's Association 2014. (Accessed 06.02. 2014) http://www.alz.org/alzheimers_disease_facts_and_figures.asp?sp=true.

30. Shaji KS. Dementia care in developing countries: The road ahead. Indian J Psychiatry. 2009; 51 Suppl 1:S5-7.

31. Wimo A , Jönsson L, Bond J, Prince M, Winblad B; Alzheimer Disease International. World Alzheimer's report 2010 the global economic impact of dementia Alzheimer's disease International. 2010.

32. Hurd MD, Martorell P, Delavande A, Mullen KJ, Langa KM. Monetary costs of dementia in the united states. N Engl J Med. 2013; 368(14):1326-1334.

33. Alzheimer's disease genetics fact sheet. Alzheimer's disease Education & Referral (ADEAR) Centre: A Service of the National Institute on Aging National Institutes of Health, U.S. Department of Health and Human Services 2014. (Accessed 26.03. 2014) http://www.nia.nih.gov/alzheimers/publication/alzheimers-disease-genetics-fact-sheet.

34. Reitz C, Mayeux R. Use of genetic variation as biomarkers for Alzheimer's disease. Ann N Y Acad Sci. 2009; 1180:75-96.

35. Skoog I, Gustafson D. Hypertension, hypertension-clustering factors and Alzheimer's disease. Neurol Res. 2003; 25(6):675-680.

36. Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, Havlik RJ. Midlife blood pressure and dementia: The Honolulu-Asia aging study. Neurobiol Aging. 2000;21(1):49–55.

37. Kivipelto M, Helkala EL, Laakso MP, Hänninen T, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A. Midlife vascular risk factors and Alzheimer's disease in later life: Longitudinal, population based study. BMJ. 2001; 322(7300):1447-1451.

38. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol. 2005; 4(8):487-499.

39. Ruitenberg A, den Heijer T, Bakker SL, van Swieten JC, Koudstaal PJ, Hofman A, Breteler MM. Cerebral hypoperfusion and clinical onset of dementia: The Rotterdam study. Ann Neurol. 2005;57(6):789–794.

40. Haag MD, Hofman A, Koudstaal PJ, Breteler MM, Stricker BH. Duration of antihypertensive drug use and risk of dementia: A prospective cohort study. Neurology. 2009; 72(20):1727-1734.

41. Wildburger NC, Lin-Ye A, Baird MA, Lei D, Bao J. Neuroprotective effects of blockers for T-type calcium channels. Mol Neurodegener. 2009;4:44.

42. Ohrui T, Tomita N, Sato-Nakagawa T, Matsui T, Maruyama M, Niwa K, Arai H, Sasaki H. Effects of brain-penetrating ACE inhibitors on alzheimer disease progression. Neurology. 2004; 63(7):1324-1325.

43. Li NC, Lee A, Whitmer RA, Kivipelto M, Lawler E, Kazis LE, Wolozin B. Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: Prospective cohort analysis. BMJ. 2010; 340:b5465.

44. Solomon A, Kareholt I, Ngandu T, Winblad B, Nissinen A, Tuomilehto J, Soininen H, Kivipelto M. Serum cholesterol changes after midlife and late-life cognition: Twenty-one-year follow-up study. Neurology. 2007; 68(10):751-756.

45. Ghribi O. Potential mechanisms linking cholesterol to Alzheimer's disease-like pathology in rabbit brain, hippocampal organotypic slices, and skeletal muscle. J Alzheimer Dis. 2008; 15(4):673-684.

46. Matsuzaki T, Sasaki K, Hata J, Hirakawa Y, Fujimi K, Ninomiya T, Suzuki SO, Kanba S, Kiyohara Y, Iwaki T. Association of alzheimer disease pathology with abnormal lipid metabolism: The Hisayama study. Neurology. 2011; 77(11):1068-1075.

47. Silva T, Teixeira J, Remiao F, Borges F. Alzheimer's disease, cholesterol, and statins: The junctions of important metabolic pathways. Angew Chem Int Ed Engl. 2013; 52(4):1110-1121.

48. Roberts RO, Geda YE, Knopman DS, Christianson TJ, Pankratz VS, Boeve BF, Vella A, Rocca WA, Petersen RC. Association of duration and severity of diabetes mellitus with mild cognitive impairment. Arch Neurol. 2008;65(8):1066-1073.

49. Xu W, Qiu C, Gatz M, Pedersen NL, Johansson B, Fratiglioni L. Mid- and late-life diabetes in relation to the risk of dementia: A population-based twin study. Diabetes. 2009; 58(1):71-77.

50. Huang CC, Chung CM, Leu HB, et al. Diabetes mellitus and the risk of Alzheimer's disease: A nationwide population-based study. PLoS One. 2014;9(1):e87095.

51. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: A systematic review. Lancet Neurol. 2006; 5(1):64-74.

52. Irie F, Fitzpatrick AL, Lopez OL, et al. Enhanced risk for Alzheimer's disease in persons with type 2 diabetes and APOE epsilon4: The cardiovascular health study cognition study. Arch Neurol. 2008; 65(1):89-93.

53. Cholerton B, Baker LD, Craft S. Insulin resistance and pathological brain ageing. Diabet Med. 2011; 28(12):1463-1475.

54. Akter K, Lanza EA, Martin SA, Myronyuk N, Rua M, Raffa RB. Diabetes mellitus and Alzheimer's disease: Shared pathology and treatment? Br J Clin Pharmacol. 2011; 71(3):365-376.

55. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam study. Neurology. 1999; 53(9):1937-1942.

56. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The nun study. JAMA. 1997; 277(10):813-817.

57. Heyman A, Fillenbaum GG, Welsh-Bohmer KA, Gearing M, Mirra SS, Mohs RC, Peterson BL, Pieper CF. Cerebral infarcts in patients with autopsy-proven Alzheimer's disease: CERAD, part XVIII. Consortium to establish a registry for Alzheimer's disease. Neurology. 1998; 51(1):159-162.

58. Honig LS, Tang MX, Albert S, Luchsinger J, Manly J, Stern Y, Mayeux R.. Stroke and the risk of Alzheimer's disease. Arch Neurol. 2003; 60(12):1707-1712.

59. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med. 2003; 348(13):1215-1222.

60. Wiesmann M, Kiliaan AJ, Claassen JA. Vascular aspects of cognitive impairment and dementia. J Cereb Blood Flow Metab. 2013; 33(11):1696-1706.

61. Aznar S, Knudsen GM. Depression and Alzheimer's disease: Is stress the initiating factor in a common neuropathological cascade? J Alzheimer's Dis. 2011; 23(2):177-193.

62. Dal Forno G, Palermo MT, Donohue JE, Karagiozis H, Zonderman AB, Kawas CH. Depressive symptoms, sex, and risk for Alzheimer's disease. Ann Neurol. 2005;57(3):381-387.

63. Andersen K, Lolk A, Kragh-Sorensen P, Petersen NE, Green A. Depression and the risk of Alzheimer's disease. Epidemiology. 2005;16(2):233–238.

64. Amieva H, Le Goff M, Millet X, Orgogozo JM, Pérès K, Barberger-Gateau P, Jacqmin-Gadda H, Dartigues JF. Prodromal Alzheimer's disease: Successive emergence of the clinical symptoms. Ann Neurol. 2008; 64(5):492-498.

65. Saczynski JS, Beiser A, Seshadri S, Auerbach S, Wolf PA, Au R. Depressive symptoms and risk of dementia: The Framingham heart study. Neurology. 2010;75(1):35-41.

66. Wint D. Depression: A shared risk factor for cardiovascular and Alzheimer's disease. Cleve Clin J Med. 2011;78 Suppl 1:S44-6.

67. Almeida OP, Hulse GK, Lawrence D, Flicker L. Smoking as a risk factor for Alzheimer's disease: Contrasting evidence from a systematic review of case-control and cohort studies. Addiction. 2002;97(1):15-28.

68. Sahakian B, Jones G, Levy R, Gray J, Warburton D. The effects of nicotine on attention, information processing, and short-term memory in patients with dementia of the alzheimer type. Br J Psychiatry. 1989; 154:797-800.

69. Merchant C, Tang MX, Albert S, Manly J, Stern Y, Mayeux R. The influence of smoking on the risk of Alzheimer's disease. Neurology. 1999;52(7):1408-1412.

70. Anstey KJ, von Sanden C, Salim A, O'Kearney R. Smoking as a risk factor for dementia and cognitive decline: A meta-analysis of prospective studies. Am J Epidemiol. 2007; 166(4):367-378.

71. Peters R, Poulter R, Warner J, Beckett N, Burch L, Bulpitt C. Smoking, dementia and cognitive decline in the elderly, a systematic review. BMC Geriatr. 2008;8:36-2318-8-36.

72. Collins MA, Neafsey EJ, Mukamal KJ, Gray MO, Parks DA, Das DK, Korthuis RJ. Alcohol in moderation, cardioprotection, and neuroprotection: Epidemiological considerations and mechanistic studies. Alcohol Clin Exp Res. 2009; 33(2):206-219.

73. Neafsey EJ, Collins MA. Moderate alcohol consumption and cognitive risk. Neuropsychiatr Dis Treat. 2011;7:465–484.

74. Anttila T, Helkala EL, Viitanen M, Kåreholt I, Fratiglioni L, Winblad B, Soininen H, Tuomilehto J, Nissinen A, Kivipelto M. Alcohol drinking in middle age and subsequent risk of mild cognitive impairment and dementia in old age: A prospective population based study. BMJ. 2004; 329(7465):539.

75. Huang W, Qiu C, Winblad B, Fratiglioni L. Alcohol consumption and incidence of dementia in a community sample aged 75 years and older. J Clin Epidemiol. 2002;55(10):959–964.

76. Ruitenberg A, van Swieten JC, Witteman JC, Mehta KM, van Duijn CM, Hofman A, Breteler MM. Alcohol consumption and risk of dementia: The Rotterdam study. Lancet. 2002; 359(9303):281-286.

77. Ding J, Eigenbrodt ML, Mosley TH,Jr, Hutchinson RG, Folsom AR, Harris TB, Nieto FJ. Alcohol intake and cerebral abnormalities on magnetic resonance imaging in a community-

based population of middle-aged adults: The atherosclerosis risk in communities (ARIC) study. Stroke. 2004; 35(1):16-21.

78. Paul CA, Au R, Fredman L, Massaro JM, Seshadri S, Decarli C, Wolf PA. Association of alcohol consumption with brain volume in the Framingham study. Arch Neurol. 2008; 65(10):s1363-1367.

79. Orgogozo JM, Dartigues JF, Lafont S, Letenneur L, Commenges D, Salamon R, Renaud S, Breteler MB. Wine consumption and dementia in the elderly: A prospective community study in the Bordeaux area. Rev Neurol (Paris). 1997; 153(3):185-192.

80. Pasinetti GM. Novel role of red wine-derived polyphenols in the prevention of Alzheimer's disease dementia and brain pathology: Experimental approaches and clinical implications. Planta Med. 2012; 78(15):1614-1619.

81. Gustafson D. Adiposity indices and dementia. Lancet Neurol. 2006; 5(8):713-720.

82. Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kåreholt I, Winblad B, Helkala EL, Tuomilehto J, Soininen H, Nissinen A.. Obesity and vascular risk factors at midlife and the risk of dementia and alzheimer disease. Arch Neurol. 2005; 62(10):1556-1560.

83. Rosengren A, Skoog I, Gustafson D, Wilhelmsen L. Body mass index, other cardiovascular risk factors, and hospitalization for dementia. Arch Intern Med. 2005; 165(3):321-326.

84. Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP,Jr, Yaffe K. Obesity in middle age and future risk of dementia: A 27 year longitudinal population based study. BMJ. 2005; 330(7504):1360.

85. Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth WT Jr, Luchsinger JA. Midlife and late-life obesity and the risk of dementia: Cardiovascular health study. Arch Neurol. 2009; 66(3):336-342.

86. Stewart R, Masaki K, Xue QL, Peila R, Petrovitch H, White LR, Launer LJ. A 32-year prospective study of change in body weight and incident dementia: The Honolulu-Asia aging study. Arch Neurol. 2005;62(1):55-60.

87. Naderali EK, Ratcliffe SH, Dale MC. Obesity and Alzheimer's disease: A link between body weight and cognitive function in old age. Am J Alzheimer's Dis Other Demen. 2009; 24(6):445-449.

88. Zandi PP, Anthony JC, Khachaturian AS, Stone SV, Gustafson D, Tschanz JT, Norton MC, Welsh-Bohmer KA, Breitner JC; Cache County Study Group. Reduced risk of Alzheimer's disease in users of antioxidant vitamin supplements: The cache county study. Arch Neurol. 2004;61(1):82-88.

89. Barberger-Gateau P, Raffaitin C, Letenneur L, Berr C, Tzourio C, Dartigues JF, Alpérovitch A. Dietary patterns and risk of dementia: The three-city cohort study. Neurology. 2007; 69(20):1921-1930.

90. Scarmeas N, Stern Y, Mayeux R, Luchsinger JA. Mediterranean diet, alzheimer disease, and vascular mediation. Arch Neurol. 2006; 63(12):1709-1717.

91. Malouf R, Areosa Sastre A. Vitamin B12 for cognition. Cochrane Database Syst Rev. 2003 ;(3) (3):CD004326.

92. Schaefer EJ, Bongard V, Beiser AS, Lamon-Fava S, Robins SJ, Au R, Tucker KL, Kyle DJ, Wilson PW, Wolf PA. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: The Framingham heart study. Arch Neurol. 2006; 63(11):1545-1550.

93. Huang TL, Zandi PP, Tucker KL, Fitzpatrick AL, Kuller LH, Fried LP, Burke GL, Carlson MC. Benefits of fatty fish on dementia risk are stronger for those without APOE epsilon4. Neurology. 2005; 65(9):1409-1414.

94. Eskelinen MH, Ngandu T, Tuomilehto J, Soininen H, Kivipelto M. Midlife coffee and tea drinking and the risk of late-life dementia: A population-based CAIDE study. J Alzheimer's Dis. 2009; 16(1):85-91.

95. Schmidt R, Schmidt H, Curb JD, Masaki K, White LR, Launer LJ. Early inflammation and dementia: A 25-year follow-up of the Honolulu-Asia aging study. Ann Neurol. 2002; 52(2):168-174.

96. Engelhart MJ, Geerlings MI, Meijer J, Kiliaan A, Ruitenberg A, van Swieten JC, Stijnen T, Hofman A, Witteman JC, Breteler MM. Inflammatory proteins in plasma and the risk of dementia: The Rotterdam study. Arch Neurol. 2004;61(5):668-672.

97. Tan ZS, Beiser AS, Vasan RS, Roubenoff R, Dinarello CA, Harris TB, Benjamin EJ, Au R, Kiel DP, Wolf PA, Seshadri S. Inflammatory markers and the risk of Alzheimer disease: The Framingham study. Neurology. 2007;68(22):1902-1908.

98. Imbimbo BP, Solfrizzi V, Panza F. Are NSAIDs useful to treat Alzheimer's disease or mild cognitive impairment? Front Aging Neurosci. 2010;2:10.3389/fnagi.2010.00019. eCollection 2010.

99. Alzheimer's Disease Anti-inflammatory Prevention Trial Research Group. Results of a follow-up study to the randomized Alzheimer's disease anti-inflammatory prevention trial (ADAPT). Alzheimers Dement. 2013;9(6):714-723.

100. Breitner JC, Baker LD, Montine TJ, Meinert CL, Lyketsos CG, Ashe KH, Brandt J, Craft S, Evans DE, Green RC, Ismail MS, Martin BK, Mullan MJ, Sabbagh M, Tariot PN; ADAPT Research Group. Extended results of the Alzheimer's disease anti-inflammatory prevention trial. Alzheimer's Dement. 2011;7(4):402-411.

101. Ong CK, Lirk P, Tan CH, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. Clin Med Res. 2007;5(1):19-34.

102. Qiu C, Karp A, von Strauss E, Winblad B, Fratiglioni L, Bellander T. Lifetime principal occupation and risk of Alzheimer's disease in the Kungsholmen project. Am J Ind Med. 2003;43(2):204-211.

103. Feychting M, Jonsson F, Pedersen NL, Ahlbom A. Occupational magnetic field exposure and neurodegenerative disease. Epidemiology. 2003; 14(4):413-9; discussion 427-8.

104. Qiu C, Fratiglioni L, Karp A, Winblad B, Bellander T. Occupational exposure to electromagnetic fields and risk of Alzheimer's disease. Epidemiology. 2004;15(6):687-694.

105. Garcia AM, Sisternas A, Hoyos SP. Occupational exposure to extremely low frequency electric and magnetic fields and Alzheimer disease: A meta-analysis. Int J Epidemiol. 2008; 37(2):329-340.

106. Fleminger S, Oliver DL, Lovestone S, Rabe-Hesketh S, Giora A. Head injury as a risk factor for Alzheimer's disease: The evidence 10 years on; a partial replication. J Neurol Neurosurg Psychiatry. 2003;74(7):857-862.

107. Mehta KM, Ott A, Kalmijn S, Slooter AJ, van Duijn CM, Hofman A, Breteler MM. Head trauma and risk of dementia and Alzheimer's disease: The Rotterdam study. Neurology. 1999;53(9):1959-1962.

108. Himanen L, Portin R, Isoniemi H, Helenius H, Kurki T, Tenovuo O. Longitudinal cognitive changes in traumatic brain injury: A 30-year follow-up study. Neurology. 2006;66(2):187-192.

109. Alcohol use after traumatic brain injury alcohol use after traumatic brain injury alcohol use after traumatic brain injury alcohol use after traumatic brain injury http://www.msktc.org/tbi/factsheets/Alcohol-Use-After-Traumatic-Brain-Injury. Updated 2011. Accessed 02/02, 2014.

110. Wang HX, Gustafson DR, Kivipelto M, Pedersen NL, Skoog I, Windblad B, Fratiglioni L. Education halves the risk of dementia due to apolipoprotein epsilon4 allele: A collaborative study from the Swedish brain power initiative. Neurobiol Aging. 2012;33(5):1007.e1-1007.e7.

111. Ferrari C, Nacmias B, Bagnoli S, Piaceri I, Lombardi G, Pradella S, Tedde A, Sorbi S. Imaging and cognitive reserve studies predict dementia in presymptomatic Alzheimer's disease subjects. Neurodegener Dis. 2014;13(2-3):157-159.

112. Scarmeas N, Stern Y. Cognitive reserve: Implications for diagnosis and prevention of Alzheimer's disease. Curr Neurol Neurosci Rep. 2004;4(5):374-380.

113. EClipSE Collaborative Members, Brayne C, Ince PG, et al. Education, the brain and dementia: Neuroprotection or compensation? Brain. 2010; 133(Pt 8): 2210–2216.

114. Liu Y, Julkunen V, Paajanen T, Westman E, Wahlund LO, Aitken A, Sobow T, Mecocci P, Tsolaki M, Vellas B, Muehlboeck S, Spenger C, Lovestone S, Simmons A, Soininen H; AddNeuroMed Consortium. Education increases reserve against Alzheimer's disease-evidence from structural MRI analysis. Neuroradiology. 2012; 54(9):929-938.

115. Mortamais M, Portet F, Brickman AM, Provenzano FA, Muraskin J, Akbaraly TN, Berr C, Touchon J, Bonafé A, le Bars E, Menjot de Champfleur N, Maller JJ, Meslin C, Sabatier R, Ritchie K, Artero S. Education modulates the impact of white matter lesions on the risk of mild cognitive impairment and dementia. Am J Geriatr Psychiatry. 2013.

116. Soldan A, Pettigrew C, Li S, Wang MC, Moghekar A, Selnes OA, Albert M, O'Brien R; BIOCARD Research Team. Relationship of cognitive reserve and cerebrospinal fluid biomarkers to the emergence of clinical symptoms in preclinical Alzheimer's disease. Neurobiol Aging. 2013; 34(12):2827-2834.

117. Crowe M, Andel R, Pedersen NL, Johansson B, Gatz M. Does participation in leisure activities lead to reduced risk of Alzheimer's disease? A prospective study of Swedish twins. J Gerontol B Psychol Sci Soc Sci. 2003;58(5):P249-55.

118. Andel R, Crowe M, Pedersen NL, Mortimer J, Crimmins E, Johansson B, Gatz M. Complexity of work and risk of Alzheimer's disease: A population-based study of Swedish twins. J Gerontol B Psychol Sci Soc Sci. 2005;60(5):P251-8.

119. Robertson IH. A right hemisphere role in cognitive reserve. Neurobiol Aging. 2014;35(6):1375-1385.

120. Wilson RS, Nag S, Boyle PA, Hizel LP, Yu L, Buchman AS, Schneider JA, Bennett DA. Neural reserve, neuronal density in the locus ceruleus, and cognitive decline. Neurology. 2013;80(13):1202-1208.

121. Heneka MT, Nadrigny F, Regen T, Martinez-Hernandez A, Dumitrescu-Ozimek L, Terwel D, Jardanhazi-Kurutz D, Walter J, Kirchhoff F, Hanisch UK, Kummer MP. Locus ceruleus controls Alzheimer's disease pathology by modulating microglial functions through norepinephrine. Proc Natl Acad Sci U S A. 2010; 107(13):6058-6063.

122. Wang HX, Wahlberg M, Karp A, Winblad B, Fratiglioni L. Psychosocial stress at work is associated with increased dementia risk in late life. Alzheimer's Dement. 2012;8(2):114-120

123. Johansson L, Guo X, Waern M, Ostling S, Gustafson D, Bengtsson C, Skoog I. Midlife psychological stress and risk of dementia: A 35-year longitudinal population study. Brain. 2010; 133(Pt 8):2217-2224.

124. Esch T, Stefano GB, Fricchione GL, Benson H. The role of stress in neurodegenerative diseases and mental disorders. Neuro Endocrinol Lett. 2002; 23(3):199-208.

125. Kesaniemi A, Riddoch CJ, Reeder B, Blair SN, Sorensen TI. Advancing the future of physical activity guidelines in canada: An independent expert panel interpretation of the evidence. Int J Behav Nutr Phys Act. 2010; 7:41-5868-7-41.

126. Nelson ME, Rejeski WJ, Blair SN, Duncan PW, Judge JO, King AC, Macera CA, Castaneda-Sceppa C. Physical activity and public health in older adults: Recommendation from the American college of sports medicine and the American heart association. Med Sci Sports Exerc. 2007;39(8):1435-1445.

127. O'Donovan G, Blazevich AJ, Boreham C, Cooper AR, Crank H, Ekelund U, Fox KR, Gately P, Giles-Corti B, Gill JM, Hamer M, McDermott I, Murphy M, Mutrie N, Reilly JJ, Saxton JM, Stamatakis E. The ABC of physical activity for health: A consensus statement from the British association of sport and exercise sciences. J Sports Sci. 2010; 28(6):573-591.

128. Grimby G. Physical activity and muscle training in the elderly. Acta Med Scand Suppl. 1986; 711:233-237.

129. Ng SW, Popkin BM. Time use and physical activity: A shift away from movement across the globe. Obes Rev. 2012; 13(8):659-680.

130. Global strategy on diet, physical activity and health. World Health Organization 2014. (Accessed 03.04.2014). http://www.who.int/dietphysicalactivity/pa/en/.

131. Sofi F, Valecchi D, Bacci D, et al. Physical activity and risk of cognitive decline: A meta-analysis of prospective studies. J Intern Med. 2011; 269(1):107-117.

132. van Gelder BM, Tijhuis MA, Kalmijn S, Giampaoli S, Nissinen A, Kromhout D. Physical activity in relation to cognitive decline in elderly men: The FINE study. Neurology. 2004; 63(12):2316-2321.

133. Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K. A prospective study of physical activity and cognitive decline in elderly women: Women who walk. Arch Intern Med. 2001; 161(14):1703-1708.

134. Rosano C, Venkatraman VK, Guralnik J, Newman AB, Glynn NW, Launer L, Taylor CA, Williamson J, Studenski S, Pahor M, Aizenstein H. Psychomotor speed and functional brain MRI 2 years after completing a physical activity treatment. J Gerontol A Biol Sci Med Sci. 2010; 65(6):639-647.

135. Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, Elavsky S, Marquez DX, Hu L, Kramer AF. Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Med Sci. 2006; 61(11):1166-1170.

136. Etgen T, Sander D, Huntgeburth U, Poppert H, Forstl H, Bickel H. Physical activity and incident cognitive impairment in elderly persons: The INVADE study. Arch Intern Med. 2010; 170(2):186-193.

137. Pesce C, Cereatti L, Forte R, Crova C, Casella R. Acute and chronic exercise effects on attentional control in older road cyclists. Gerontology. 2011; 57(2):121-128.

138. Taylor AH, Faulkner G. Inaugural editorial. Mental Health and Physical Activity. 2008; 1(1):1-8.

139. Cairney J, Hay JA, Wade TJ, Faught BE, Flouris A. Developmental coordination disorder and aerobic fitness: Is it all in their heads or is measurement still the problem? Am J Hum Biol. 2006; 18(1):66-70.

140. Sergeant JA, Piek JP, Oosterlaan J. ADHD and DCD: A relationship in need of research. Hum Mov Sci. 2006; 25(1):76-89.

141. Uda M, Ishido M, Kami K, Masuhara M. Effects of chronic treadmill running on neurogenesis in the dentate gyrus of the hippocampus of adult rat. Brain Res. 2006; 1104(1):64-72.

142. Olson AK, Eadie BD, Ernst C, Christie BR. Environmental enrichment and voluntary exercise massively increase neurogenesis in the adult hippocampus via dissociable pathways. Hippocampus. 2006; 16(3):250-260.

143. Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, Webb A, Jerome GJ, Marquez DX, Elavsky S. Cardiovascular fitness, cortical plasticity, and aging. Proc Natl Acad Sci U S A. 2004; 101(9):3316-3321.

144. Yoshitake T, Kiyohara Y, Kato I, Ohmura T, Iwamoto H, Nakayama K, Ohmori S, Nomiyama K, Kawano H, Ueda K. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: The Hisayama study. Neurology. 1995; 45(6):1161-1168.

145. Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FM, Xiao J, Greenop KR, Almeida OP. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: A randomized trial. JAMA. 2008; 300(9):1027-1037.

146. Adlard PA, Perreau VM, Pop V, Cotman CW. Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. J Neurosci. 2005; 25(17):4217-4221.

147. Liang KY, Mintun MA, Fagan AM, Goate AM, Bugg JM, Holtzman DM, Morris JC, Head D. Exercise and Alzheimer's disease biomarkers in cognitively normal older adults. Ann Neurol. 2010; 68(3):311-318.

148. Sutoo D, Akiyama K. Regulation of brain function by exercise. Neurobiol Dis. 2003; 13(1):1-14.

149. Hattori S, Naoi M, Nishino H. Striatal dopamine turnover during treadmill running in the rat: Relation to the speed of running. Brain Res Bull. 1994; 35(1):41-49.

150. Winter B, Breitenstein C, Mooren FC, Voelker K, Fobker M, Lechtermann A, Krueger K, Fromme A, Korsukewitz C, Floel A, Knecht S. High impact running improves learning. Neurobiol Learn Mem. 2007; 87(4): 597-609.

151. Sarbadhikari SN, Saha AK. Moderate exercise and chronic stress produce counteractive effects on different areas of the brain by acting through various neurotransmitter receptor subtypes: A hypothesis. Theor Biol Med Model. 2006; 3:33.

152. van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat Neurosci. 1999; 2(3):266-270.

153. Farmer J, Zhao X, van Praag H, Wodtke K, Gage FH, Christie BR. Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male sprague-dawley rats in vivo. Neuroscience. 2004; 124(1):71-79.

154. van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc Natl Acad Sci U S A. 1999; 96(23):13427-13431.

155. Gertz K, Priller J, Kronenberg G, Fink KB, Winter B, Schröck H, Ji S, Milosevic M, Harms C, Böhm M, Dirnagl U, Laufs U, Endres M. Physical activity improves long-term stroke outcome via endothelial nitric oxide synthase-dependent augmentation of neovascularization and cerebral blood flow. Circ Res. 2006; 99(10):1132-1140.

156. Endres M, Gertz K, Lindauer U, Katchanov J, Schultze J, Schröck H, Nickenig G, Kuschinsky W, Dirnagl U, Laufs U. Mechanisms of stroke protection by physical activity. Ann Neurol. 2003; 54(5):582-590.

157. Prasad S, Sung B, Aggarwal BB. Age-associated chronic diseases require age-old medicine: Role of chronic inflammation. Prev Med. 2012; 54 Suppl: S29-37.

158. Carro E, Torres-Aleman I. The role of insulin and insulin-like growth factor I in the molecular and cellular mechanisms underlying the pathology of alzheimer's disease. Eur J Pharmacol. 2004; 490(1-3):127-133.

159. Brisswalter J, Collardeau M, Rene A. Effects of acute physical exercise characteristics on cognitive performance. Sports Med. 2002; 32(9):555-566.

160. Tomporowski PD. Effects of acute bouts of exercise on cognition. Acta Psychol (Amst). 2003; 112(3):297-324.

161. Tappen RM, Roach KE, Applegate EB, Stowell P. Effect of a combined walking and conversation intervention on functional mobility of nursing home residents with alzheimer disease. Alzheimer Dis Assoc Disord. 2000; 14(4):196-201.

162. Cohen-Mansfield J, Mintzer JE. Time for change: The role of nonpharmacological interventions in treating behavior problems in nursing home residents with dementia. Alzheimer Dis Assoc Disord. 2005; 19(1):37-40.

163. Stevens J, Killeen M. A randomised controlled trial testing the impact of exercise on cognitive symptoms and disability of residents with dementia. Contemp Nurse. 2006; 21(1):32-40.

164. Landi F, Russo A, Bernabei R. Physical activity and behavior in the elderly: A pilot study. Arch Gerontol Geriatr Suppl. 2004 ;(9) (9):235-241.

165. Biddle S, Fox K, Boutcher S. Physical activity and psychological well-being. Physical activity and psychological well-being. 2001.

166. Biddle S, Ekkekakis P. Physically active lifestyles and well-being. In: F. A. Huppert, B. Keverne, N. Baylis, eds. The science of well-being. Oxford, UK: Oxford University Press; 2005:140-168.

167. Plowman S A, Smith D L. Neuroendocrine contol of exercise. In: Exercise physiology for health, fitness, and performance. 2nd ed. Lippincott Williams & Wilkins; 2007:61.

168. Shamliyan T, Kane RL, Jansen S. Quality of systematic reviews of observational nontherapeutic studies. Prev Chronic Dis. 2010; 7(6):A133.

169. Shamliyan T, Kane RL, Dickinson S. A systematic review of tools used to assess the quality of observational studies that examine incidence or prevalence and risk factors for diseases. J Clin Epidemiol. 2010; 63(10):1061–1070.

170. Shamliyan TA, Kane RL, Ansari MT, Raman G, Berkman ND, Grant M, Janes G, Maglione M, Moher D, Nasser M, Robinson KA, Segal JB, Tsouros S. Development quality criteria to evaluate nontherapeutic studies of incidence, prevalence, or risk factors of chronic diseases: Pilot study of new checklists. J Clin Epidemiol. 2011; 64(6):637-657.

171. Epidemiological research methods. The Pennsylvania State University 2014. (Accessed 6.24.2014) https://onlinecourses.science.psu.edu/stat507/node/68.

172. de Bruijn RF, Schrijvers EM, de Groot KA, Witteman JC, Hofman A, Franco OH, Koudstaal PJ, Ikram MA. The association between physical activity and dementia in an elderly population: The Rotterdam study. Eur J Epidemiol. 2013; 28(3):277-283.

173. Buchman AS, Boyle PA, Yu L, Shah RC, Wilson RS, Bennett DA. Total daily physical activity and the risk of AD and cognitive decline in older adults. Neurology. 2012; 78(17):1323-1329.

174. Verdelho A, Madureira S, Ferro JM, Baezner H, Blahak C, Poggesi A, Hennerici M, Pantoni L, Fazekas F, Scheltens P, Waldemar G, Wallin A, Erkinjuntti T, Inzitari D; LADIS Study. Physical activity prevents progression for cognitive impairment and vascular dementia: Results from the LADIS (leukoaraiosis and disability) study. Stroke. 2012; 43(12):3331-3335.

175. Scarmeas N, Luchsinger JA, Schupf N, Brickman AM, Cosentino S, Tang MX, Stern Y. Physical activity, diet, and risk of Alzheimer disease. JAMA. 2009; 302(6):627-637.

176. Taaffe DR, Irie F, Masaki KH, Abbott RD, Petrovitch H, Ross GW, White LR. Physical activity, physical function, and incident dementia in elderly men: The Honolulu-Asia aging study. J Gerontol A Biol Sci Med Sci. 2008; 63(5):529-535.

177. Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P, Kukull W. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med. 2006; 144(2):73-81.

178. Podewils LJ, Guallar E, Kuller LH, Fried LP, Lopez OL, Carlson M, Lyketsos CG. Physical activity, APOE genotype, and dementia risk: Findings from the cardiovascular health cognition study. Am J Epidemiol. 2005; 161(7):639-651.

179. Rovio S, Kareholt I, Helkala EL, Viitanen M, Winblad B, Tuomilehto J, Soininen H, Nissinen A, Kivipelto M. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. Lancet Neurol. 2005; 4(11):705-711.

180. Abbott RD, White LR, Ross GW, Masaki KH, Curb JD, Petrovitch H. Walking and dementia in physically capable elderly men. JAMA. 2004; 292(12):1447-1453.

181. Lindsay J, Laurin D, Verreault R, Hébert R, Helliwell B, Hill GB, McDowell I. Risk factors for Alzheimer's disease: A prospective analysis from the Canadian study of health and aging. Am J Epidemiol. 2002; 156(5):445-453.

182. Verghese J, Lipton RB, Katz MJ, Hall CB, Derby CA, Kuslansky G, Ambrose AF, Sliwinski M, Buschke H. Leisure activities and the risk of dementia in the elderly. N Engl J Med. 2003; 348(25):2508-2516.

183. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch Neurol. 2001; 58(3):498-504.

184. Scarmeas N, Levy G, Tang MX, Manly J, Stern Y. Influence of leisure activity on the incidence of Alzheimer's disease. Neurology. 2001; 57(12):2236-2242.

185. Ravaglia G, Forti P, Lucicesare A, Pisacane N, Rietti E, Bianchin M, Dalmonte E. Physical activity and dementia risk in the elderly: Findings from a prospective Italian study. Neurology. 2008; 70(19 Pt 2):1786-1794.

186. Rovio S, Kareholt I, Viitanen M, Winblad B, Tuomilehto J, Soininen H, Nissinen A, Kivipelto M. Work-related physical activity and the risk of dementia and alzheimer's disease. Int J Geriatr Psychiatry. 2007; 22(9):874-882.

187. Yamada M, Kasagi F, Sasaki H, Masunari N, Mimori Y, Suzuki G. Association between dementia and midlife risk factors: The radiation effects research foundation adult health study. J Am Geriatr Soc. 2003; 51(3):410-414.

188. Wilson RS, Bennett DA, Bienias JL, Aggarwal NT, Mendes De Leon CF, Morris MC, Schneider JA, Evans DA. Cognitive activity and incident AD in a population-based sample of older persons. Neurology. 2002; 59(12):1910-1914.

189. Godin G, Shephard RJ. A simple method to assess exercise behavior in the community. Can J Appl Sport Sci. 1985; 10(3):141-146.

190. Caspersen CJ, Bloemberg BP, Saris WH, Merritt RK, Kromhout D. The prevalence of selected physical activities and their relation with coronary heart disease risk factors in elderly men: The Zutphen study, 1985. Am J Epidemiol. 1991; 133(11):1078-1092.

191. Kannel WB, Sorlie P. Some health benefits of physical activity. The Framingham study. Arch Intern Med. 1979; 139(8):857-861.

192. Garcia-Palmieri MR, Costas R,Jr, Cruz-Vidal M, Sorlie PD, Havlik RJ. Increased physical activity: A protective factor against heart attacks in Puerto rico. Am J Cardiol. 1982; 50(4):749-755.

193. Jetté M, Sidney K, Blümchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. Clin Cardiol. 1990; 13(8):555-565.

194. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr, Schmitz KH, Emplaincourt PO, Jacobs DR Jr, Leon AS. Compendium of physical activities: An update of activity codes and MET intensities. Med Sci Sports Exerc. 2000; 32(9 Suppl):S498-504. 201.

195. Sattler C, Erickson KI, Toro P, Schroder J. Physical fitness as a protective factor for cognitive impairment in a prospective population-based study in germany. *J Alzheimers Dis.* 2011; 26(4):709-718.

196. Manson JE, Greenland P, LaCroix AZ, Stefanick ML, Mouton CP, Oberman A, Perri MG, Sheps DS, Pettinger MB, Siscovick DS. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. N Engl J Med. 2002; 347(10):716-725.

197. Lee IM. No pain, no gain? Thoughts on the Caerphilly study. Br J Sports Med. 2004; 38(1):4-5.

198. Sesso HD, Paffenbarger RS,Jr, Lee IM. Physical activity and coronary heart disease in men: The Harvard Alumni Health Study. Circulation. 2000; 102(9):975-980.

199. Thompson PD, Buchner D, Pina IL, Balady GJ, Williams MA, Marcus BH, Berra K, Blair SN, Costa F, Franklin B, Fletcher GF, Gordon NF, Pate RR, Rodriguez BL, Yancey AK, Wenger NK; American Heart Association Council on Clinical Cardiology Subcommittee on Exercise, Rehabilitation, and Prevention; American Heart Association Council on Nutrition, Physical Activity, and Metabolism Subcommittee on Physical Activity. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: A statement from the council on clinical cardiology (subcommittee on exercise, rehabilitation, and prevention) and the council on nutrition, physical activity, and metabolism (subcommittee on physical activity). Circulation. 2003; 107(24):3109-3116.

200. Fratiglioni L, Wang HX. Brain reserve hypothesis in dementia. J Alzheimer's Dis. 2007; 12(1):11-22.

201. Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: Key roles of growth factor cascades and inflammation. Trends Neurosci. 2007; 30(9):464-472.

202. Richardson MT, Leon AS, Jacobs DR,Jr, Ainsworth BE, Serfass R. Comprehensive evaluation of the Minnesota leisure time physical activity questionnaire. J Clin Epidemiol. 1994; 47(3):271-281.

203. Cotman CW, Engesser-Cesar C. Exercise enhances and protects brain function. Exerc Sport Sci Rev. 2002; 30(2):75-79.

204. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: A meta-analytic study. Psychol Sci. 2003; 14(2):125-130.

205. Kramer AF, Erickson KI. Capitalizing on cortical plasticity: Influence of physical activity on cognition and brain function. Trends Cogn Sci. 2007; 11(8):342-348.

206. Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: A systematic review of prospective evidence. Psychol Med. 2009; 39(1):3-11.

207. Rolland Y, Abellan van Kan G, Vellas B. Physical activity and Alzheimer's disease: From prevention to therapeutic perspectives. J Am Med Dir Assoc. 2008; 9(6):390-405.